STUDIES BEARING ON

(I) THE NUTRITION OF BANTU INFANTS AND YOUNG CHILDREN

AND

(II) THE METABOLISM OF CALCIUM AND IRON

BY BANTU CHILDREN AND ADULTS

BY

ALEXANDER ROBERT PETTIGREW WALKER

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GENERAL INDEX. PAGE.

(The above page sequence does not take into account the pages of the actual papers published or in press, i.e. the papers included in sections 4,8, and 12.)

STUDIES BEARING ON (I) THE NUTRITION OF BANTU INFANTS AND CHILDREN, AND (II) THE METABOLISM OF CALCIUM AND IRON BY BANTU CHILDREN AND ADULTS.

PART I: STUDIES BEARING ON THE NUTRITION OF TRANSVAAL BANTU INFANTS AND CHILDREN.

PART I: STUDIES BEARING ON THE NUTRITION OF BANTU INFANTS AND CHILDREN

1. INTRODUCTION.

The continent of Africa is inhabited by about 270 million persons of whom about 60 million are Bantu. They dwell mainly south of the Equator. South African Bantu number about 11 million persons, of whom under a third are urbanised, and over a third each work on farms of Whites or live in the Native Reserves. These local Bantu are comprised of several ethnic groups, the largest of which are Zulu and Xhosa. While some communities of rural Bantu still live in a primitive manner, others, mainly in urban areas, tend progressively to adopt a westernised type of diet and manner of life. These Bantu may therefore be observed in all stages of transition, in relation to patterns of diet, metabolism, and pathology. The studies undertaken and to be described concern primarily the nutrition of infants and children, the prevalence of certain deficiency diseases, and the handicap imposed by parasitism on nutritional state and other parameters.

2. STUDIES ON INFANT NUTRITION.

By far the most serious health problem among the Bantu concerns the high mortality and morbidity prevailing among the very young. The problem is most acute at weaning time and thereafter. It must be stressed, however, that although undernutrition and malnutrition are important factors in this adverse picture, a large measure of responsibility must be borne by ignorance, and by the operation of non-nutritional environmental factors (e.g. infections from overcrowding and poor hygiene, etc.).

(i) The composition of Bantu breast milk (major nutrients)[1,2]

Analysis of a large number of samples of breast milk from Bantu mothers reveals the mean chemical composition to be similar in most respects to that of White mother's milk.

N.B. The reference numbers apply wholly to the writer's publications.

Since Bantu mothers have milk of satisfactory composition and almost invariably lactate well, it is not surprising that for the first 6 months of life, Bantu babies grow as rapidly, sometimes more rapidly, than White babies. Afterwards, when the yield of breast milk is insufficient for nutritional needs, and when weaning foods are nutritionally inadequate (see later), the state of health and rate of growth deteriorate.

(ii) Low niacin concentration in Bantu breast milk.[3]

Since experimental studies on small animals have indicated that part of the niacin in maize is present in a form not readily available for metabolism, it was thought worthwhile to determine if the concentration of this nutrient in the milk of Bantu mothers was prejudiced when they consume a diet high in maize products. This was found to be the case. The lower concentration of the nutrient, however, is still higher than that present in the mixture of 2 parts cow's milk to 1 part water, which has been used so extensively and successfully in the artificial feeding of White babies.

(iii) Methionine concentration in Bantu breast milk.[4]

Arising from a report from West Africa that the level of methionine ~~was~~ is low in the breast milk of mothers consuming a low protein diet (mainly of vegetable origin), a study was made of the concentration of this amino acid in Bantu breast milk. Results showed the latter to have the same mean amount of methionine (and tryptophane) that has been found in milk from White mothers.

(iv) Composition of food mixtures used in the weaning of Bantu infants.[5]

In the classic report of Brock and Autret on "Kwashiorkor in Africa" (1951) attention was drawn to the deleterious effects of the consumption of thin gruels of cereals and other local foods so frequently used in the weaning of African infants. In seeking to throw further light on the

problem, we found that the mixtures used by Bantu mothers in Johannesburg for weaning their babies almost invariably are defective in calories and in most nutrients.

3. STUDIES BEARING ON THE PREVALENCE AND OTHER ASPECTS OF DEFICIENCY DISEASES IN YOUNG BANTU.

(i) Kwashiorkor: the relationship of nutritional oedema and sweating.[6]

Probably the earliest balance studies on kwashiorkor patients in South Africa were undertaken by the writer in collaboration with Dr. E. Khan of Baragwanath Hospital. But since it rapidly became apparent that superior facilities and more satisfactory observations were being undertaken by Professor J.F. Brock and Dr. J.D.L. Hansen at Cape Town University, and Professor J.G.A. Davel and Dr. P.J. Pretorius at Pretoria University, the balance studies at Baragwanath Hospital were terminated. A study, however, on the relationship between nutritional oedema and sweating in kwashiorkor patients during recovery was carried out in association with Dr. Khan and reported. Observations showed that as the oedema subsided, the sweating mechanism, previously inhibited, tended to return to normal.

(ii) The rarity of scurvy in Bantu infants and children.[7]

Scurvy in weaned Bantu infants and young children is extremely rarely seen in patients admitted to Non-European Hospitals on the Witwatersrand. Our findings of satisfactory levels of vitamin C in the plasma of groups of such persons is consistent with the virtual absence of the disease. Nevertheless, the source of the vitamin C, whether ingested, or, as has been even hazarded, synthesized, remains a mystery.

(iii) Rickets in Bantu infants and young children in urban and rural areas.[8]

Studies on Bantu infants, carried out in association with paediatricians from Coronation Hospital (Drs.H.C. Falke, H. Cohen and A. Nestadt), indicate that where advantage be taken

of available radiation, rickets presents no serious problem. Thus, the disease is common in urban Bantu infants, but rare in those dwelling in rural areas. (The situation is discussed further in Part II, in the section dealing with calcium metabolism in the Bantu). Two specialized studies dealing with parathyroid function in rickets[9.10] were carried out in association with Dr. L.S. Taitz, Baragwanath Hospital; the Unit was primarily responsible for the biochemical determinations involved.

(iv) The rarity of Bitot's spots in Bantu school children.

Bitot's spots have been seen in an eye of a Bantu child once only out of some 10,000 children examined over a period of several years and during the course of carrying out many different types of study. The rarity, locally, of the stigma, whose aetiology remains unknown although initially ascribed to vitamin A deficiency, contrasts with its commonness elsewhere in Africa and India; for example, in one recent study reported from Bombay, 4 per cent of children were affected.

(v) The uncommonness of iron deficiency anaemia in Bantu school children.[11]

Haemoglobin (and to a lesser extent haematocrit) levels have been determined on several thousands of Bantu school children in different regions in the Transvaal. The general picture is that iron deficiency anaemia is very uncommon. Comparative values are given in Tables 4 and 5. Attention is drawn to our finding that at an altitude near sea level, at Komatipoort, Eastern Transvaal, mean haemoglobin levels of post-adolescent boys and girls were 14.6 ± 1.3 g./% and 13.8 ± 1.1 g./%, respectively, despite the presence of both types of bilharzia in over two thirds of the children studied (Tables 4 and 5). By any standards, such levels are very satisfactory. Higher than average haemoglobin levels

have been found in children at a school in a Native Reserve near Rustenburg, and somewhat lower than average values have been found in a school at Louis Trichardt. Both these Bantu child populations are being further investigated. The commendable values found in most Bantu children probably stem from their relatively high iron intake (see Part II). It has been found that high mean haemoglobin values in groups of subjects (although not individuals) correlate with higher than average iron concentration in their stools, and vice versa. The foregoing picture, which is in harmony with that found by Dr. M.L. Neser in studies recently undertaken on several hundred Bantu school children in Pretoria, stands in marked contrast to the high prevalence of iron deficiency anaemia reported by Dr. P.L. Lankowsky in Bantu pre-school children in Cape Town, also the high prevalences found in numerous studies on indigenous populations in other parts of Africa, also Middle and Far Eastern countries.

(vi) The prevalence of clinical nutritional stigmata in groups of Bantu school children.[12]

Dr. S.D. Mistry (Indian physician) has carried out clinical studies on the pupils of several rural and urban schools in respect of growth, lesions of skin, mouth and eyes, musculature, and other parameters. It was found, broadly, that whereas the frequency of stigmata differed from school to school, and from area to area, in groups of pupils before puberty, differences were far less marked after puberty. Indeed, in Johannesburg, for example, it was found that school groups of older pupils (15 + years) presented much the same nutritional picture, almost irrespective of the socio-economic level of the respective neighbourhoods.

(vii) Comment.

No studies have been carried out on beri-beri, since the disease extremely rarely occurs in the Bantu. No research

work has been undertaken on the biochemistry of pellagra in the young, because other South African workers, especially those at the C.S.I.R. National Nutrition Research Institute, Pretoria, have been and still are engaged on the problem.

In summary, among Bantu children, by far the most serious nutritional deficiency disease in kwashiorkor. The metabolic aspects of its causation and treatment are now well understood, this being due in large part to the pioneer studies carried out at Cape Town. Morbidity from scurvy, rickets, and iron deficiency anaemia is slight, although that from pellagra still remains a health problem. While there is good knowledge of the nutritional aspects of these diseases (causation and treatment), the metabolic and other aspects still require much further research.

4. DIETARY, ANTHROPOMETRIC, BIOCHEMICAL, AND OTHER STUDIES ON BANTU CHILDREN IN VARIOUS REGIONAL AND SOCIO-ECONOMIC GROUPS.

As indicated in the Introduction, at present South African Bantu may be observed in all stages of transition - primitive and sophisticated, indigent and better class, rural and urban. To throwlight on the changing situation, various investigations, as opportunity offers, have been carried out.

(i) Diet.[13]

Only general observations are being made with regard to diet, in view of the far more detailed studies now being undertaken by the Field Studies Group of the C.S.I.R. National Nutritional Research Institute, Pretoria. Rough appraisal, however, reveals that the diet of privileged Bantu conforms in large measure to that of the poorer section of the White population. Information touching on the changes in regard of intakes of calories, protein, fat, calcium, and iron, is given in subsequent sections.

(ii) Rate of growth: Skinfold changes.[14,15,16]

Many studies on growth have been carried out within the last ten years on different school child groups. At present, measurements are being made, not only of height and weight, but of arm girth and of skin folds (triceps, scapula, iliac, and umbilicus). Observations indicate that: (a) Current data on height and weight are significantly superior to such measured ten years ago. (b) In the better class groups, e.g. Bantu children attending urban Secondary Schools, both sexes have much the same mean height and weight as ~~Canadian~~ London Council School children (Poor group) measured in ~~1953~~ 1945. (c) In respect of skin-folds, better class Bantu girls, although not boys, attain mean values exceeding those given in reports on contemporary White girls. While there is an insufficiency of calories among many of the young in rural areas, it is possible that a proportion of the better class urban groups have an excess of calories. On the other hand body fat distribution may differ ethnically in Bantu and whites. Representative data are given in Tables 1 - 3.

(iii) Onset of menarche.[16]

Inquiries are being pursued regarding the mean time of commencement of menstruation in groups of Bantu girls differing in ethnic grouping, locality (urban, rural), nutritional state, environmental temperature, and in other respects. While primitive indigent rural groups have a mean starting time of as late as 15.1 years, better class urban groups (e.g. Secondary School girls) have a starting time almost the same as that of overseas English girls, namely, 13.2 - 13.6 years.

(iv) Haematological studies.[11]

This aspect has been discussed earlier, where attention was drawn to the very low prevalence of iron deficiency anaemia in Transvaal Bantu school children. Representative data are given in Tables 4 and 5.

(v) Urinary nitrogen excretion and nitrogen partition. [17]

Series of 24-hour urine samples have been collected from pupils in different schools, usually from groups of 10 boys and 10 girls of ages 16-18 years, i.e. post-puberty subjects. Observations indicate mean urinary excretions of 7 - 8 g. nitrogen per diem in the poorer schools, and 9 - 10 g. nitrogen in the better class schools. In Macy's study in U.S.A., the daily range for young American children was given as 7.8 - 11.0 g.; and in the well known investigations of McCance and Widdowson on German children at Wuppertal, a mean figure of 9.5 g. nitrogen in the urine was found. Thus, the figures on the Bantu groups studied compare not unfavourably with those reported for overseas White children. The excretions of the Bantu are much higher than such obtaining among groups of children in other parts of Africa and in India. Regarding nitrogen partition in the urine, initial studies have been reported on groups of Bantu, Indian and White children. Determinations were made of urea nitrogen/total nitrogen percentage, and urea/creatinine ratio. The subject is being pursued further in view of certain anomalies that have been encountered. One point has become clear, however, namely, that in the same individual, the indices vary considerably from day to day; hence, in respect of single spot urine sample collections, only mean values for groups of subjects may be used for comparative purposes.

(v) Serum protein fractionation: liver function tests. [16]

Representative data on these parameters are given in Table 6. Studies show higher serum protein levels in urban compared with rural groups, paralleling level of ~~intake of protein~~ nitrogen excretion (also, of course, paralleling superiority in height and weight data, earlier time of onset of menarche, etc.) Regarding serum gamma globulin, it is noteworthy that:-

(a) In rural groups, mean values are significantly lower than such determined 10 years ago. (b) In both rural and urban areas

mean values are lower in upper class compared with poor Bantu. (c) Mean values are higher in bilharzial compared with non-bilharzial areas. These conclusions also apply, not unexpectedly, to the liver function tests carried out (Table 6).[19] In addition to the latter tests mentioned, several other liver function tests have been carried out, although the number of subjects studied is not yet sufficient to warrant comment. Representative data are given in Table 6.

(vii) Serum Lipid levels.[16]

Data on serum cholesterol levels are given in Table 7. Levels for Secondary School Bantu children are only slightly lower than such on local White children. Levels of serum phospholipid, beta-lipoprotein, and triglycerides, as expected, are low, means of 210 mg., 120 mg., and 40 mg./%, respectively, having been obtained for rural population groups.

(viii) Other biochemical parameters.[16]

(a) Urinary excretion of calcium. Studies in groups of pupils (10 boys and 10 girls) in six schools, have given excretions of 30 - 75 mg. calcium per 24 hours. These values are much lower than those prevailing with White children. (b) Urinary excretion of sodium chloride. Average daily excretions averaged about 9 g. salt. ~~Intakes~~ Excretions differed only slightly from school to school. (c) Urinary steroid excretion. Limited data on the excretion of 17-ketosteroids and 17-hydroxy-corticosteroids in 24-hour urine samples reveal that mean levels of both components are lower in Bantu compared with White children. This finding has been reported for other less privileged groups. (d) Urinary excretion of albumin. Excretions are lower in magnitude and in frequency in children in urban compared with rural regions, and, not surprisingly, are lower in school groups without bilharzia, compared with those with bilharzia. Even in groups with intense urinary bilharzia, however, the excretion of albumin is less frequent than in such groups in Central Africa. (e) Sugar in urine. The excretion of sugar is very rare in Bantu children; never more than a

trace has been encountered in several thousands of urine samples examined.

(ix) Blood pressures.

Representative data are given in Table 8. Pressures appear to rise with socio-economic state, and with urbanisation. They are higher in certain groups of girls than in boys.

5. FOREWORD TO TABLES ILLUSTRATING CHANGES IN VARIOUS PARAMETERS IN BANTU CHILDREN.

The following tables are given to provide a general picture of the observations already referred to; they will be included in future publications. However, it must be emphasized that:-

(i) The data given are not complete.

(ii) The numbers in certain groups of persons studied will require to be considerably augmented.

(iii) The appropriate statistical treatment will be given.

(i) Methods employed in the obtaining of data given in the tables or referred to previously.

Heights and weights. The height and weight figures refer to subjects without shoes on, but wearing their everyday clothes.

Blood pressures. These were determined on subjects in the sitting position. In the measurement of diastolic pressure, the disappearance of sound was taken as the end point. While usually three measurements of pressures were made, the data reported must be taken as referring to "casual" pressures.

Haematology. Erythrocyte sedimentation rate was determined by the Wintrobe method. The tubes were spun at 3,000 r.p.m. for ½ hour to obtain packed cell volume. Haemoglobin determination were carried out by the oxyhaemoglobin method, and read from a graph constructed using a sample of known haemoglobin concentration. The graph was further checked by determining the iron concentration in a series of bloods, and from such values calculating haemoglobin concentrations.

Protein fractionation and liver function tests. Total serum protein was determined by the micro-Kjeldahl method. The fractionation was undertaken by paper electrophoresis, using Beckman Spinco cells, staining with bromo-phenol blue (methanol solution), and scanning with the Spinco Analytrol. Thymol turbidity was determined using the method of MacLagan (Brit. J. Exp. Path., 26, 234, 1944), and thymol flocculation by the method of Neefe and Rheinhold (Gastroenterology, 7, 393, 1946).

Serum Lipids. The following methods were used:-

Serum cholesterol (Pearson, modified by Van Boetzer and Zondag, Clin. Chim. Acta, 5, 943, 1960).

Phospholipid (Fiske and Subbarow, J. Biol. Chem., 66, 1943, 1960).

Beta-lipoprotein (Burstein et al. Clin. Chem. Acta., 5, 943, 1960).

Triglycerides (Van Handel and Zilversmit, J. Lab. Clin. Med., 50, 152, 1957).

Glycosuria. Glycosuria was detected using Clinistix, Tes-tape, also Clinitest for semi-quantitative estimation.

Albuminuria. Albustix was used.

17-ketosteroids and 17-hydroxy-corticosteroids. Formerly, the methods followed were mainly those of Norymberski et al. (Lancet, i, 1276, 1953) and others. More recently, the methods evolved by the M.R.C. Committee have been adopted (Lancet, i, 1415, 1963).

TABLE 1.

MEAN DATA ON HEIGHT, WEIGHT, AND ARM GIRTH OF GROUPS OF BANTU BOYS AT 14-15 YEARS

Population Groups	No. of Subjects	Height (in.) Mean & S.D.	Weight (lb.) Mean & S. D.	Arm Girth (in.) Mean & S.D.
Rural.				
Poor Primary School. Tswana. (1954)	15	55.7 2.2	67.2 14.1	7.3 0.8
Ditto. (1964)	18	58.1 2.4	75.1 15.2	7.5 0.7
Higher Primary School. Tswana. (1963)	28	58.3 2.3	77.3 14.9	7.7 0.9
Primary School. Zulu. (1963)	19	58.5 2.5	86.0 15.1	8.1 0.8
Secondary School Tswana (1963)	28	59.5 2.4	80.6 14.4	8.0 1.0
Urban.				
Poor Primary School. Mixed. (1964)	38	59.7 2.5	87.2 14.2	8.1 0.9
Higher Primary School. (1963)	46	59.9 2.3	90.3 13.9	8.3 0.8
Secondary School. (1964)	55	60.8 2.4	104.3 14.7	8.2 1.0
Cape Town. Whites. (1958)[1]		62.75	102.0	
London. Council School. (Poor) (1945-52)[2]		61.0	99.7	
Canada. (1953)[3]		62.2	107	
Iowa. U.S.A. (1945)[4]		63.2	113.0	

N.B. 14-15 years implies the period 14.00 - 14.99 years.

1. Lurie,G.M., and Ford,F.J. S.Afr.Med.J., 32: 1017, 1958.
2. Hammond,W.H. Brit.J.Prev.Soc.Med., 7: 231, 1953.
3. Pett,L.B., and Ogilview,G.F. In: Body Measurements and Human Nutrition. Ed.J.Brozek. Wayne University Press,Detroit, Mitchigan, 1956.
4. Eppright,E.S., and Sidwell,V.D. J.Nutr., 54: 543, 1954.

TABLE 2

MEAN DATA ON HEIGHT, WEIGHT, AND ARM GIRTH OF GROUPS OF BANTU GIRLS 14-15 YEARS

Population Group.	No. of Subjects	Height (in.) Mean & S.D.	Weight (lb.) Mean & S.D.	Arm Girth (in.) Mean & S.D.
Rural.				
Poor Primary School. Tswana. (1954)	15	57.9 2.4	72.0 13.9	7.9 0.8
Ditto. (1964)	18	58.3 2.3	81.4 14.2	8.1 0.7
Higher Primary School. Tswana. (1963)	24	59.1 2.5	84.6 15.1	8.3 0.9
Primary School. Zulu. (1963)	19	59.6 2.4	94.1 14.9	8.8 0.8
Secondary School. Tswana. (1963)	24	59.7 2.5	90.2 14.7	9.0 0.9
Urban.				
Poor Primary School. Mixed. (1964)	25	60.2 2.4	96.4 14.6	8.8 0.8
Higher Primary School. (1963)	28	60.5 2.6	97 .6 15.1	9.0 1.0
Secondary School. (1964)	41	60.9 2.5	109.1 14.7	8.8 0.9
Cape Town. Whites. (1958)[1]		62.5	104.0	-
London. Council School. (Poor) (1945-52)[2]		60.2	100 8	-
Canada. (1953)[3]		61.3	107.0	-
Iowa. U.S.A. (1945)[4]		62.7	113.0	-

TABLE 3

MEAN DATA ON SKIN FOLD MEASUREMENTS OF BANTU SCHOOL CHILDREN

BOYS

Population Group	No. of Subjects	Skinfolds (mm.)			
		Triceps	Scapula	Iliac	Umbilicus
Rural.					
Poor Primary School. 10-11 years.	17	6.3	5.1	4.4	4.4
Higher Primary School. 15-17 years.	27	6.6	6.6	6.6	6.5
Urban.					
Poor Primary School. 10-11 years.	22	6.4	5.2	5.6	4.9
Higher Primary School. 15-17 years.	25	6.7	6.5	6.8	6.6
Secondary School. 15-17 years.	26	8.4	7.7	7.6	8.1
London. Government School. 15-17 years.[1]		7.5	7.7	-	-
United States High School. 14.5-18.5 years.[2]	36	10.5	10.0	-	-

References:-

1. Tanner, J.M. and Whitehouse, R.H. Standards for subcutaneous fat in British children. Brit. Med. J., i: 446, 1962.

2. Novak, L.P. Age and sex differences in body density and creatinine excretion of high school children. Ann. New York Acad. Sci., 110: 545, 1963.

TABLE 3A

MEAN DATA ON SKIN FOLD MEASUREMENTS OF BANTU SCHOOL CHILDREN

GIRLS

Population Group	No. of Subjects	Skinfolds (mm.)			
		Triceps	Scapula	Iliac	Umbilicus
Rural.					
Poor Primary School. 10-11 years.	19	7.4	5.1	5.1	5.7
Higher Primary School. 15-17 years.	31	13.3	10.4	9.4	12.4
Urban.					
Poor Primary School. 10-11 years.	17	9.2	5.9	5.7	6.4
Higher Primary School. 15-17 years.	35	15.2	10.7	11.8	12.1
Secondary School. 15-17 years.	45	21.3	15.6	12.4	15.6
London Government School. 15-17 years.[1]		14.0	10.5	-	-
United States. High School. 14.5-18.5 years.[2]	32	16.5	10.2	-	-

TABLE 4.

MEAN HAEMOGLOBIN CONCENTRATIONS IN GROUPS OF BANTU CHILDREN AT 10-12 YEARS

Population Group	Boys		Girls	
	No. of Subjects	Haemoglobin g.%.	No. of Subjects	Haemoglobin g.%.
RURAL. 4000-6000 ft.				
Primary School	24	14.5	18	14.4
Higher Primary School	27	14.8	21	14.6
URBAN. 4000-6000 ft.				
Primary School	29	15.1	26	14.9
Higher Primary School	33	15.4	29	15.0
URBAN. 4000-6000 ft.				
White children	25	15.1	20	14.8
RURAL. 1000 ft.				
Primary School. (Bantu)	36	13.4	36	13.1
Dutch children.[1] (12 years)	22	13.5	109	13.4
Norwegian children.[2] (10-13 years)		13.2		13.1
U.S.A. White children[3] (12 years)		13.0		13.0

References:-

1. De Vijn. Ned. T. Geneesk., 105: 1028, 1961.

2. Natvig, H., Bjerkedal, T., and Jonassen, O. Acta Med. Scand., 174: 351, 1963.

3. Leichsering, J.M., Norris, L.M., Lamison, S.A., and Halbert, M.L. Amer. J. Dis. Child., 90: 159, 1955.

TABLE 5.

MEAN HAEMOGLOBIN CONCENTRATIONS IN GROUPS OF BANTU SCHOOL CHILDREN AT 16-18 YEARS OLD

Population Group	Boys		Girls	
	No. of Subjects	Haemoglobin g.%.	No. of Subjects	Haemoglobin g.%.
RURAL. 4000-6000 ft.				
Higher Primary School	25	15.5	19	14.6
Secondary School	22	15.8	21	15.2
URBAN. 4000-6000 ft.				
Higher Primary School	21	16.4	39	15.1
Secondary School	25	17.6	25	15.3
URBAN. 1000 ft.				
Primary School. Bantu	31	14.6	13	13.8
Dutch children. (16-17 years.)[1]	152	14.75	240	13.6
U.S.A. White children. (16 years)[3]	-	15.1	-	13.0

TABLE 6

MEAN DATA ON SERUM PROTEIN FRACTIONATION AND LIVER FUNCTION TESTS IN GROUPS OF BANTU BOYS AND GIRLS

Population Group	Total Serum Protein g./%	Serum Albumin g./%	Serum Globulin g./%	Globulin Fractions g./%				Serum Thymol Turbidity	Serum Thymol Flocculation
				α_1	α_2	β	γ		
Rural 1	6.95	3.25	3.70	0.29	0.72	0.81	1.88	70%	84%
	0.49	0.38	0.41	0.08	0.17	0.16	0.35	< 2	-ve
2	6.78	3.07	3.71	0.27	0.71	0.79	1.94	67%	79%
	0.55	0.44	0.45	0.11	0.19	0.18	0.38	< 2	-ve
Urban 1	7.25	3.80	3.42	0.33	0.69	0.75	1.65	72%	88%
	0.51	0.42	0.39	0.09	0.16	0.14	0.32	< 2	-ve
Whites.	6.85	3.85	3.00	0.30	0.70	0.85	1.15		
	0.48	0.51	0.42	0.08	0.15	0.13	0.36		

Rural 1. Poor and middle class children. 19 boys, 17 girls. Ages 14 - 16 years.

2. Poorer children in bilharzial region. 17 boys, 16 girls. Ages 13 - 16 years.

Urban 1. Poor and middle class children. 21 boys, 17 girls. Ages 15 - 17 years.

Whites White South African children. 12 boys, 9 girls. Ages 14 - 16 years.

TABLE 7. MEAN DATA ON SERUM CHOLESTEROL CONCENTRATION IN GROUPS OF BANTU BOYS AND GIRLS

Population Group	Age Group (years)	No. of subjects	Serum Cholesterol g./.%	
			Mean	S.D.
Rural:				
Poor Primary School.	12-15	25 boys 20 girls	144 149	41 43
Higher Primary School.	12-16	31 boys 21 girls	149 153	39 42
Secondary School.	13-16	19 boys 20 girls	160 167	46 47
Urban:				
Poor Primary School.	12-15	25 boys 21 girls	165 174	49 51
Higher Primary School.	12-16	27 boys 24 girls	181 201	47 45
Secondary School.	13-16	25 boys 25 girls	195 211	43 48
South African White Children	13-16	12 boys 13 girls	222 231	39 37

TABLE 8

MEAN DATA ON BLOOD PRESSURE OF GROUPS OF BANTU BOYS AND GIRLS AT 14 - 15 YEARS

Population Group	Sex	No. of subjects	Systolic pressure mm. Hg.		Diastolic pressure mm. Hg.	
			Mean	S.D.	Mean	S.D.
Rural						
Poor Primary School	Boys	18	104	12.1	54	8.0
	Girls	18	114	11.6	61	7.9
Higher Primary School	Boys	28	106	11.1	58	9.0
	Girls	24	112	12.4	63	8.6
Secondary School	Boys	28	107	10.8	63	7.9
	Girls	24	119	11.4	69	8.5
Urban						
Poor Primary School	Boys	38	106	10.2	59	8.7
	Girls	25	119	13.0	62	9.2
Higher Primary School	Boys	46	107	10.9	63	7.7
	Girls	28	118	10.8	66	8.5
Secondary School	Boys	55	115	11.7	65	8.4
	Girls	41	123	12.7	71	9.2
South African White School Children	Boys	24	117	11.7	71	9.8
	Girls	21	116	12.5	72	9.3

6. STUDIES BEARING ON THE HANDICAP IMPOSED BY PARASITISM ON NUTRITIONAL STATE.

(i) Common helminths in the stools of various groups of Bantu children.[18]

Following an early study (1952), much further work has been carried out recently. It has been found that a very high proportion of highveld school children are virtually free from helminths (as low as 5 per cent ascaris present). The proportion with this type of infection is higher in children in peri-urban areas, and still higher in urban areas, where a prevalence of 50 - 60 per cent of pupils with ascaris was reached in some of the groups examined. In coastal regions, e.g. Illovo, near Durban, and Chicumbane, north of Lourenco Marques, Mocambique, parasitism is very widespread, virtually every child being infected, often with several types of parasites. Thus, while helminthiasis (excluding Schistosoma mansoni) presents little public health problem in most inland highveld regions, it remains a health problem in urban areas, also in lowveld and coastal regions, both rural and urban.

(ii) Blood loss in schistosoma haematobium infection.[19]

It was found that in subjects with heavy infections of vesical bilharzia, blood loss was 1-6 ml. per diem. While this amount, especially if intermittent, is unlikely to cause a significant anaemia, it may well aggravate an existing anaemia.

(iii) Blood loss in schistosoma mansoni infection.[20]

Although studies show the blood loss in intestinal bilharzia to be slight, it is possible that other features of this infection affect haemopoiesis.

(iv) Blood loss in ancylostomiasis infection.[21]

Studies on blood loss in hookworm infection, revealed blood loss in severe cases to be of the order of 9 - 19 ml. per diem.

This finding has been amply confirmed by reports from later workers.

(v) Various studies in school-child population groups, with and without bilharzia.[22,23]

Studies in this field of research are undertaken as opportunity offers. For a number of years, the Unit has been endeavouring to carry out comparative studies on groups of Bantu school children, firstly, in areas where bilharzia is common, and secondly, in areas where it is absent. These studies have been pursued in respect of rate of growth, onset of menarche, motor fitness (Harvard Step Test), haematology, blood biochemistry, nutritional stigmata, scholastic ability, and other parameters. While these investigations are still in progress, the tentative conclusion has been reached that, in the age groups studied, and with the intensity of infection prevailing, the handicap is less than expected. In S. haematobium infection, and to a somewhat lesser extent in S. mansoni infection, it has been found that rate of growth and skinfold measurements provide much the same picture in groups with and without bilharzia. Concerning haematology, haemoglobin levels may be 0.5 - 1.0 g.% lower in the infected; however, anaemia, when present, is slight. Serum gamma globulin is significantly elevated in the infected. On the other hand, observations indicate that motor fitness, also scholastic ability, are often higher in the infected, suggesting that it is the more adventurous child who goes further afield and becomes infected.

The extent of the morbidity from bilharzia in human beings remains a subject of controversy. That ill-effects can result is indisputable; but evidence suggests that they involve only a minority of sufferers. Uncertainties in respect of prognosis and of treatment are understandable, since no prospective studies have been undertaken in which the health status of those infected has been matched (age, sex, environment, occupation, etc.) against those not infected.

Furthermore, in respect of treatment, there have been no investigations in which the response (clinical, subjective, etc.) to drugs has been compared with that of placebos.

The field and laboratory studies described are being continued. Obviously, a considerable amount of further work on carefully selected populations will be required before it is possible to speak with some measure of certainty on the handicap imposed by certain parasites on nutritional and other aspects of the health picture. It must be understood, ~~of course,~~ moreover, that the conclusions reached will be valid fully only for the population groups investigated, and that caution will be required in the extrapolation of the conclusions to other populations.

SUMMARY OF PART I AND SUGGESTIONS FOR FUTURE RESEARCH

1. Each of the papers published or in press, on which the standard of this work is judged, has its own summary. The following comments are therefore wholly general.

2. The studies on Bantu infants and young children concern three aspects, namely, (i) the nutrition of breast fed and weaned children, (ii) the prevalence of deficiency stigmata, and the characterisation (anthrompometric, biochemical, etc.) of children differing in region, diet, socio-economic state, etc., and (iii) the bearing of parasitism, particularly bilharziasis, on the parameters cited in (ii). The second and third aspects are closely interrelated.

The studies of the writer, and of previous and present South African workers, have more than touched the fringe of the research field under consideration. It will be apparent, however, that a great deal more investigational work remains to be undertaken, before the maximum of fundamental and practical knowledge of nutritional science may be derived from the situation presented by the different local populations.

The following points seem particularly worthy of study:-

(i) Enquiry into the "cost" of repeated pregnancies and long lactations to poorly nourished Bantu mothers. (ii) Elucidation of the weaning practices of Indian mothers to account for the uncommonness of kwashiorkor in Indian young children. (iii) Determination of the reason for the rarity of scurvy in Bantu infants. (iv). Determination of the minimum excretion of urinary nitrogen per 24 hours in groups of younger and older Bantu children compatible with freedom from nutritional deficiency stigmata. (v). Elucidation of the increased loss of nitrogen (thereby affecting dietary protein requirement) from children dwelling in hot compared with cooler regions. (vi). Clarification of the urinary steroid excretion pattern in post-adolescent Bantu children on different nutritional and socio-economic planes.

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PART I.

STUDIES BEARING ON THE NUTRITION OF BANTU INFANTS AND CHILDREN.

COPIES OF PAPERS PUBLISHED OR IN PRESS.

Letter to the Editor

reprinted from THE LANCET, *February* 9, 1952, *p.* 317

BREAST-FEEDING AND DIET

SIR,—The well-known research-worker on human milk, Dr. I. G. Macy, has stated that "when the necessary ingredients for the synthesis of milk are lacking in the daily food, the mother's output of milk may be decreased, or the milk may become deficient in these constituents, or the needed elements may be withdrawn from her body tissues." [1]

The diet recommended for nursing mothers is known too well to need description.[2] The question naturally arises as to the lactation capacity of the vast majority of the world's mothers who simply do not consume such a diet. Is their milk insufficient, or of poor quality? Is the withdrawal of the needed elements—for example, of calcium—attended by deleterious effects? It is interesting to note that under very adverse conditions of diet and environment, breast-feeding may be maintained with a varying degree of success. This was observed at Belsen concentration camp,[3] at Leningrad during the siege,[4] in starving Holland in 1945,[5] in the prisoner-of-war camp at Singapore,[6] and at similar places. But the drawback is that data on the yield and composition of milk produced under such conditions are not available.

Information on the breast-milk of South African Bantu mothers is thus of interest, firstly because the great majority of these mothers are wholly able to breast-feed their infants for 6 months or longer; and secondly, because the high-cereal diet, although seldom deficient in calories, is inadequate in various respects according to accepted standards; certainly the mothers do not get the recommended allowances of milk, butter, eggs, meat, and fruit. Breast-milks were obtained from 200 urban

1. Macy, I. G., Williams, H. H., Pratt, J. P., Hamil, B. M. *Amer. J. Dis. Child.* 1945, **70**, 135.
2. McLester, J. M. Nutrition and Diet in Health and Disease. Philadelphia, 1944.
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5. Smith, C. A. *Ibid*, p. 229.
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Bantu mothers, differing in state of health, age, parity, and month of lactation. For total solids, protein, fat, lactose, ash, calcium, and phosphorus the ranges have been found to be as wide as those reported elsewhere; but our averages are almost identical to those given for white mothers by Dr. Macy.[7] The vitamin-C contents are somewhat lower, but the rarity of scurvy among urban Bantu infants suggests that the amount provided is adequate for protection. In an earlier study on 12 Bantu milks (over 1 month post partum), Mr. M. Kropman[8] found the average value for vitamin A to be slightly higher, and for carotene, thiamine, and riboflavine slightly lower, than those given for white mothers.[7] While subsequent work may well confirm that the breast-milk of urban Bantu mothers has much the same average composition (for the nutrients determined) as that of white mothers, it must be borne in mind that the nutritional value of breast-milk may not be accurately reflected by such chemical composition. As far as we are aware, no attempt has been made to compare by biological assay the nutritional value of normal milk from a malnourished mother with that from a well-nourished mother. For the nutrients we determined, no correlation was apparent between the nutritional state of the mother, as assessed by the clinic medical officers, and the composition of the breast-milk.

This capacity of these Bantu mothers to produce apparently normal milk, and wholly to breast-feed infants for long periods, raises some interesting points. Firstly, presumably the amount produced, speaking generally, is sufficient for the infant. Writing from Central Africa, Dr. H. C. Trowell[9] has stated:

> "Liberal breast feeding . . . allows the child to grow well during the first six months. . . . Provided gruels have not been given too early . . . the African baby appears to approximate to that of the European about the end of the sixth month; he is happy and playful, and for one brief period in his life, he achieves parity."

7. Macy, I. G., Kelley, H., Sloan, R. The Composition of Milks. National Research Council Bulletin, Washington, no. 119, 1950.
8. Kropman, M. Studies in Vitamin Content of African Foodstuffs. M.SC. thesis, University of South Africa. 1946.
9. Trowell, H. C. *E. Afr. med. J.* 1948, 25, 236.

Local pædiatricians agree with this observation. Next, concerning the mother, it is noteworthy that this ability to breast-feed occurs in the absence of the highly nourishing diet usually recommended. Since the lactation does not appear to be accompanied by an obvious loss in weight, it would seem unlikely that the mother's intake of gross protein is seriously insufficient. Further, with regard to calcium, their intake is meagre; yet, despite the drain that must take place, we have not found serum values for calcium to be low in prolonged lactation, and neither tetany nor osteomalacia is reported. Has it been satisfactorily established that the maternal loss of calcium in lactation is deleterious per se, and that an endeavour must be made to avoid or minimise it at all costs?

Assuming that our observations are confirmed by subsequent work, we suggest that either the rôle of diet in lactation is over-emphasised, or, alternatively, the body has a greater capacity to adapt itself to an inferior diet than is usually believed. Our observations also suggest that the low incidence of breast-feeding among western white mothers can seldom be attributed specifically to the consumption of a poor diet. While it is gratifying to know that the present diet of these Bantu mothers does not prejudice the satisfactory performance of the particular function of lactation, it must not be inferred that we therefore consider their diet to be adequate.

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Nutrition Unit, Council for Scientific and Industrial Research, South African Institute for Medical Research, Johannesburg.

A. R. P. WALKER
ULLA B. ARVIDSSON
W. L. DRAPER.

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THE COMPOSITION OF BREAST MILK OF SOUTH AFRICAN BANTU MOTHERS

BY

A. R. P. WALKER, M.SC., PH.D.*

ULLA B. ARVIDSSON, B.SC.

AND

W. L. DRAPER, B.SC.

Human Biochemistry Unit of the South African Institute for Medical Research, Johannesburg, and South African Council for Scientific and Industrial Research.

Our knowledge of the factors which control lactation is still far from complete. This is evident from the discussions on the subject held by the Nutrition Society (1944); from the recent survey of the literature by GUNTHER and STANIER (1950); and from other relevant publications.

It is interesting to note that anomalies are most common among Western mothers accustomed to a good or fairly adequate diet. Thus, in a study at Aberdeen on a group of well-to-do mothers, 80 per cent. were practising breast feeding after 6 months (MACKINTOSH, 1944); among a similar group in Illinois, the corresponding figure reported was 7 per cent. (BLESSING, 1937). Again, for the mothers in the frequently quoted Toronto study, the figure was 38 per cent. (EBBS and KELLEY, 1942), a figure less than the 41 per cent. reported for war-time English mothers in a poor district at Ilford (GORDON, 1942).

Under conditions of severe food deprivation and mental stress, however, anomalies are fewer. Thus, at Belsen concentration camp (ABELS, 1949), in Leningrad during the seige (ANTONOV, 1947), in starving Holland in 1945 (SMITH, 1947), in the prisoner-of-war camp at Singapore (WILLIAMS, 1946), and at similar places, breast feeding was carried out with an unexpected degree of success. Furthermore, in Holland, evidence suggested that neither quality nor yield was radically affected (SMITH, 1947).

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The majority of the world's mothers are non-White, but unfortunately there is very little quantitative information available on either the composition or the yield of their breast milk. We were therefore prompted to secure data on the milk of South African Bantu mothers, our desire being stimulated, moreover, by the following points. (1) The capacity to breast feed, often for protracted periods, is almost invariable. (2) Local pediatricians consider that for the first six months there is parity in growth and general health between European and Bantu babies when exclusively breast fed. In Uganda, TROWELL (1948) has made a like observation. These impressions suggest that for nutritional value and yield, Bantu milk closely resembles milk from European mothers. (3) The usual diet, broadly speaking, is based on maize, bread and legumes; although the diet is probably adequate in calories and gross protein, it is unsatisfactory in various respects according to accepted standards: certainly the mothers do not get the milk, butter, eggs, meat, fruit, etc. usually recommended for lactating mothers (MCLESTER and DARBY, 1952).

The composition has therefore been determined of the breast milk of Bantu mothers living in different parts of South Africa.

SUBJECTS AND METHODS

In breast-milk studies, it is desirable, either to have the total amount of milk produced over 24 hours, or to have the total amount that can be expressed from a breast at one feed time. Neither of these courses was practicable with our subjects. All our results concern " spot " samples. Self-demand feeding, however, is the rule among non-White mothers, i.e. there are no long intervals between daytime feeds, so that differences in composition between " fore " and " hind " milk are thereby minimized. Most of the mothers were feeding their infants at the time of sampling. Milk was obtained from both breasts.

A total of 266 milks were examined, these being derived from mothers dwelling in the following regions :—Witwatersrand, Transvaal (urban Bantu), 181; near Pretoria, Transvaal (peri-urban), 36; Swaziland, 10; Bechuanaland, 39 (including 10 from Lobatsi, and 29 from Tsane in South Central Kalahari Desert, i.e. 15 Bakgalagadi, six Hottentot, and eight Bushman mothers). The lactation period varied from 1 to 24 months. The clinical state, assessed by medical officers, was as follows :—poorly nourished, 31; average state of nutrition, 190; well nourished 45. About 50 ml. were usually collected, generally without difficulty. When smaller amounts were available, certain analyses had to be curtailed. Samples were stored in dark bottles in a cool place. On occasions when immediate analysis was impossible, a few drops of 10 per cent. formalin were added as preservative.

Total solids, ash, protein, calcium and phosphorus were determined by methods described by MCCANCE and SHIPP (1933), and MCCANCE et al. (1936). Fat was determined by the Rose Gottlieb method, with occasional checks by the Werner Schmidt method, both as outlined by COX (1950). Vitamin C determinations when undertaken were carried out within an hour of collection, by the dichlorophenol-indophenol method as described by the Association of Vitamin Chemists (1947).

Results are summarized in the following table. Also included for comparison are data for milks from British and American mothers given by KON and MAWSON (1950) and MACY (1949), respectively.

TABLE. Results : Composition of Bantu breast-milk.

Constituent.	*Bantu milks.* (Present series).	*British milks.*	*American milks.*
Total solids g.%	12.8 ± 1.8 266* (8.1 — 18.0)	13.7 R 12.95 S	12.9 ± 1.1 610 (10.3 — 17.5)
Ash g.%	0.20 ± 0.02 266 (0.14 — 0.28)	— —	0.20 ± 0.018 390 (0.16 — 0.27)
Protein g.%	1.35 ± 0.40 230 (0.60 — 2.25)	(33) 1.19 ± 0.52 R	1.06 ± 0.46 583 (0.73 — 2.00)
Fat g.%	3.90 ± 1.41 145 (1.10 — 9.25)	(612) 4.78 ± 1.47 R (129) 3.91 ± 1.42 S	4.54 ± 1.00 408 (1.34 — 8.29)
Lactose by difference g.%	7.10 ± 0.55 145 (5.05 — 9.45)	(616) 6.95 ± 0.35	6.8 ± 0.6 313 (5.0 — 9.2)
Calcium mg.%	28.7 ± 6.1 250 (14.0 — 47.4)	29.9 ± 4.2 76 (19.3 — 40.1)	34.4 ± 6.7 628 (17.3 — 60.9)
Phosphorus mg.%	15.2 ± 3.2 85 (7.5 — 24.0)	13.0 ± 1.9 76 (10.2 — 19.8)	14.1 ± 2.5 628 (6.8 — 26.8)
Vitamin C. mg.%	2.9 ± 1.5 135 (0.0 — 7.4)	3.6 ± 1.38 1116 (0.0 —)	5.2 ± 1.9 (233) 233 (0.0 — 11.2)

(* denotes no. of samples. R. = Reading. S. = Shoreditch)

DISCUSSION

The table reveals our mean values in all cases (save for vitamin C) to be very close to the means given for Western mothers.

We found little difference in mean composition between milks from the different regional or racial groups of mothers. This finding, however, must be regarded as tentative for the Hottentot and Bushman groups, where the numbers examined were unfortunately small.

As mentioned previously (WALKER et al. 1952), we have been unable to trace a correlation between milk composition and nutritional state of the mother. JELLIFFE (1952) has made the same observation for Nigerian mothers concerning breast milk protein concentration.

No alteration in composition was apparent on comparing data from the period 1 - 9 months (186 milks) with data from the 9th month onward (90 milks). Here again, JELLIFFE (1952) has made the same observation for the protein concentration of the milk of Nigerian mothers, a finding at variance with the often expressed view that protein concentration diminishes rapidly towards the end of lactation (WRIGHT, 1952).

Attention is drawn to certain aspects of our data.

Protein. Our average figure is slightly higher than the values given for Western mothers; moreover, it is also higher than the mean value given for Dakar mothers' milks, namely, 1.24 per cent., by DUFOUR and GOURRY (1934).

Fat. DEEM (1931) and later workers found that the fat content of human milk could be increased by raising the fat content of the mothers' diet. CLEMENTS (1949) reported that when the percentage of fat is initially high, it is possible to reduce it by dietary means. But

the extent to which fat restriction or habitually low intakes of fat influence its concentration in breast milk is uncertain, conflicting observations having been reported (SALMI, 1944; VON SYDOW, 1945). The mean figure for our Bantu mothers cannot be regarded as low. Our dietitian, Miss J. L. SEWARD, estimated the range of fat intake to be 20-50 g. per diem. This finding is of interest bearing in mind that an average of 30 g. fat are secreted daily in 750 ml. Bantu breast milk, the approximate daily yield at 6 months.

Calcium. The mean calcium concentration, also the range of values, are both close to data reported for Western mothers. As noted previously, the Bantu are habituated to a diet low in calcium (WALKER, 1951).

Vitamin C. Our mean value is low, yet agrees with earlier data given by KROPMAN (1946) for 36 Johannesburg Bantu mothers, and by SQUIRES (1952) for Tswana (Bechuanaland) mothers' milks. Very low values were frequent and even zero values were occasionally encountered; yet infantile scurvy is extremely rare. Thus, at a local non-European hospital, in a 5-year period, there have been three cases of scurvy out of 5,000 admissions of children under 1 year (KAHN, 1953).

In a thesis not readily accessible, KROPMAN (*loc. cit.*) reported that in an examination of 29-37 milks from Johannesburg Bantu mothers, be found the average value for vitamin A to be slightly higher, and for carotene thiamin, and riboflavin to be slightly lower than mean values given for Western mothers. Data on other vitamins, also certain amino acids (particularly tryptophane and methionine) are being obtained at this Unit. Nevertheless, in view of the good nutritional state of exclusively breast-fed Bantu babies, it would seem reasonable to consider that even if subsequent investigation reveals certain specific differences in composition, such differences are of little nutritional importance.

Arising from this capacity of these Bantu mothers to produce apparently normal milk and wholly to breast-feed infants for long periods, we are driven to conclude that either the rôle of diet in lactation is over-emphasized, or, alternatively, that the body has a greater capacity to adapt itself to an inferior diet than is usually accepted. In particular, our observations indicate that the low incidence of breast feeding among Western mothers can very seldom be attributed to the consumption of a poor diet.

Naturally, it may be wondered whether the nutritional state of the Bantu mothers is adversely affected by prolonged lactation. As far as we are aware the problem even among Western mothers has not been critically investigated. We are endeavouring to obtain relevant information upon Bantu mothers on the nutritional changes occurring during the period from before pregnancy until late in lactation. At present, the consensus of opinion among experienced medical officers is that there is no obvious impairment in health.

Finally, while it is gratifying to know that the present diet of these Bantu mothers does not prejudice the satisfactory performance of the particular function of lactation, it must not be inferred that we therefore consider their diet to be adequate.

SUMMARY

Two hundred and sixty-six samples of breast milk mainly from urban South African Bantu mothers have been analysed. In respect of total solids, ash, protein, fat, lactose, calcium and phosphorus, it has been found that mean values closely approximate to corresponding means given for the milks of British and American mothers. The composition of the milks does not appear to be influenced by the tribal group of the mothers, by their habitual

diet (largely composed of maize, bread, legumes), nor by their nutritional state. Their capacity to breast-feed is almost invariable, moreover, impressions suggest that the yield is satisfactory at least for the first 6 months. It is submitted that either the rôle of diet in lactation is over-emphasized, or that the body has a greater capacity to adapt itself to an inferior diet than is usually accepted.

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Low Niacin Concentration in the Breast Milk of Bantu Mothers on a High-Maize Diet

GOLDSMITH and co-workers[1] prepared wheat and maize diets containing equal, though relatively small, amounts of niacin and tryptophan, 4·7 and 190 mgm. per diem respectively; when fed to human subjects, only those consuming the maize diet developed pellagra. In view of this abnormality of metabolism on the maize diet, it has been considered worth while to investigate whether a diet containing this cereal causes any abnormality in the concentrations of niacin and tryptophan in breast milk. Available information suggests that the level of niacin in the breast milk of White mothers is relatively independent of dietary intake[2]. In South Africa, however, Kropman[3] found twelve Bantu breast milks to contain an average of 108 μgm. niacin per 100 ml.; this average is low in comparison with the mean value of 183 μgm. obtained for the milks of 268 American mothers[4]. Kropman[3], unfortunately, provided no dietary information on the mothers concerned—an important point in the present issue, since the consumption of maize by the Bantu varies enormously, one report giving a range of 6–20 oz. per diem for urban dwellers[5].

To throw light on the subject, breast milks from four groups of mothers have been investigated: (1) Urban Bantu mothers in poor circumstances whose consumption of maize meal (90–100 per cent extraction) exceeded 1 lb. per diem, and supplied 65–85 per cent of total calories; (2) Indian and Eurafrican mothers consuming a small though variable amount of maize; (3) Bantu and Indian mothers accustomed to an almost Europeanized diet; (4) European mothers in comfortable circumstances who served as controls. Milk from groups 1–3 mothers were obtained, mainly from 10.30 a.m. to noon, when subjects were attending clinics for routine examination of their infants or themselves. All collections were 'spot' samples. Nevertheless, self-demand feeding is the rule among non-White mothers, that is, differences in composition between 'fore' and 'hind' milks are thereby minimized. Niacin was determined microbiologically by the method described by György[6]. Tryptophan determinations were carried out—on milks from groups 1 and 4 mothers only—by the microbiological method of Greene and Black[7]. Estimations of intakes of niacin

INTAKES AND BREAST MILK CONCENTRATIONS OF NIACIN AND TRYPTOPHAN OF BANTU AND OTHER MOTHERS

Group of mothers	Niacin		Tryptophan	
	Intake (mgm./ diem)	Breast milk (μgm./ 100 ml.)	Intake (mgm./ diem)	Breast milk (mgm./ 100 ml.)
1. Bantu (high-maize diet)	15–18	70±51 (38)* (15–140)	550–850	23±6 (18)* (11–33)
2. Indian and Eurafrican	not estimated	105±45 (15)* (50–175)	not estimated	not estimated
3. Bantu and Indian (European-ized diet)	not estimated	150±52 (8)* (85–270)	not estimated	not estimated
4. European	9·5–15	175±48 (8)* (110–295)	1,100–1,400	21±4·5 (12)* (13–29)

* Number of milks examined.

and tryptophan were calculated, using local[8] and American[9] food tables respectively, from dietary information collected by our dietitian, Miss J. L. Seward. These data, together with results of the determinations of these nutrients in the breast milks, are given in the table.

Digestion of group 1 breast milks with *N* sodium hydroxide for 10 min. at room temperature caused no increase in niacin concentration; hence, the vitamin is present wholly in 'unbound' or available form[10]. The difference between the means of the niacin concentrations in groups 3 and 4 mothers is not significant; in this respect, therefore, the racial factor is unimportant.

The salient observation is that, despite a probably higher intake of total niacin, the mean niacin concentration in breast milk of the high-maize Bantu mothers is much lower than the mean value for the combined groups 3 and 4 mothers consuming the European diet. The difference is statistically highly significant ($P < 0{\cdot}001$). Calculation reveals the loss of niacin in the breast milk to be small in comparison with total niacin intake—approximately 5 per cent for group 1 mothers at the third month of lactation.

Considering the results as a whole: first, wide variations of niacin concentration occur within groups, as with other constituents[11]; secondly, mean niacin concentrations increase with decreasing maize consumption. Obviously, it would be erroneous to interpret differences in niacin concentration in terms of maize intake only. However, it would seem reasonable to regard the unusually low concentration of the vitamin in Bantu breast milk as reflecting a further abnormality of niacin metabolism under conditions of high maize intake. Whether the ab-

normality is due to a large proportion of ingested niacin being 'bound', or to suppression of intestinal biosynthesis of the vitamin, or to other causes, requires further investigation.

The low intake of niacin by Bantu breast-fed babies is not apparently deleterious, for local pediatricians aver that there is parity of growth and general health between Bantu and European babies when exclusively breast-fed up to six months.

There is no statistical difference between the mean concentrations of tryptophan in the breast milks of the Bantu and European mothers (groups 1 and 4).

The determinations of niacin and tryptophan were carried out by Mr. G. Smith and Miss H. S. P. Snyman, of the South African Bureau of Standards, Pretoria. This communication is published with the permission of the South African Council for Scientific and Industrial Research.

A. R. P. WALKER

Human Biochemistry Unit,
South African Council for
Scientific and Industrial Research,
South African Institute for Medical Research,
Johannesburg. Oct. 17.

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Methionine Concentration in South African Bantu Breast Milk

BY MARIANNE ANDERSSON AND A. R. P. WALKER
Human Biochemistry Unit, South African Institute for Medical Research, Johannesburg, and South African Council for Scientific and Industrial Research

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Although going under different names, the disease commonly referred to as kwashiorkor is of world-wide distribution affecting infants and young children fed on diets habitually deficient in amino-acids. According to Brock & Autret (1952), the syndrome usually includes fatty infiltration, cellular necrosis, or fibrosis of the liver. These authors have reported that in West Africa, fibrosis of the liver may develop in infants at the age of 6 months and possibly even earlier while they are still getting the whole of their food from the breast. It has, therefore, been postulated that a factor or factors may be missing from, or deficient in, the breast milk during the first 6 months of lactation. The fact that experimental methionine deficiency in the rat results in a fatty liver (McHenry & Patterson, 1944) raises the question whether a deficiency of this amino-acid may be involved in the causation of kwashiorkor. It is thus of interest that Auffret & Tanguy (1949) have reported that the breast milk of West African mothers of Dakar is low in methionine. They found a mean value of 16 mg/100 ml., which is unusually low in comparison to the mean value of 29 mg/100 ml. quoted by them for American mothers examined by Block (1945). However, more recently, Srinivasan & Ramanathan (1954) have examined the milks of twenty-five Indian mothers, both mothers and babies being apparently healthy, and also of six Indian mothers whose children were suffering from kwashiorkor. No abnormality was apparent; for the milks from the two groups of mothers, they found average values of 29·1 and 30·4 mg methionine/100 ml. respectively. In South Africa we have found no abnormality in the mean protein concentration of Bantu breast milk (Walker, Arvidsson & Draper, 1954); moreover, the stigmata of kwashiorkor are not observed in exclusively breast-fed infants. But in view of the report from West Africa, it was thought worth while to carry out determinations of methionine in the breast milk of both Bantu and South African European mothers.

EXPERIMENTAL

Subjects and methods

'Spot' samples of breast milk were collected from twenty-nine Bantu mothers at urban and rural health clinics while mothers were waiting, mainly for the routine examination of their babies. Periods of lactation varied from 1 to 27 months. The mothers, whom the clinic medical officers judged to be representative, were in apparent good health. For purposes of comparison, twenty-five samples of breast milk were

collected from South African European mothers, also in apparent good health, by municipal health visitors during their periodic visits to mothers' homes. Periods of lactation varied from 2 weeks to 10 months.

Methionine was determined by the chemical method described by McCarthy & Sullivan (1941).

RESULTS

Our results are summarized in Table 1. Values for the methionine concentration in breast milk from groups of other mothers are included for comparison.

Table 1. *Mean methionine concentration in the breast milk of groups of Bantu and other mothers*

(Results expressed as mg methionine/100 ml. milk)

Group of mothers	Method of determination	No. of samples	Mean value and its standard deviation	Range
	Present work			
Bantu mothers	McCarthy & Sullivan (1941)	29	29·7 ± 5·1	19·6–39·0
South African European mothers	McCarthy & Sullivan (1941)	25	26·2 ± 3·2	19·3–33·4
	Other data			
Indian mothers, apparently healthy	McCarthy & Sullivan (1941)	25	29·1	—
Indian mothers with kwashiorkor babies (Srinivasan & Ramanathan, 1954)	McCarthy & Sullivan (1941)	6	30·4	—
American mothers (Williamson, 1944)	McCarthy & Sullivan (1941)	500	29	—
American mothers (Block, 1945)	McCarthy & Sullivan (1941)	—	29	—
American mothers (Beach, Bernstein, Hoffman, Teague & Macy, 1941)	Baernstein (1936)	—	18·1	—
American mothers (Macy, 1949)	Microbiological (details unpublished)	24	11·6 ± 2·3	6·5–16·0
Dakar West African mothers (Auffret & Tanguy, 1949)	Polonovski & Issartel (1948)	10	16·4	12·0–26·0

DISCUSSION

Our results show that the mean concentration of methionine in Bantu breast milk, although closely similar to, is significantly higher ($P < 0{\cdot}01$) than, the mean value for the milk of South African European mothers. Mean values are in close agreement with those given for Indian mothers, also for the American mothers studied by Williamson (1944) and Block (1945). The same method of determination, i.e. that of McCarthy & Sullivan (1941), was used in all these studies. The disagreement with the mean values reported by other groups of workers may well be due to the different methods of determination employed. It is possible, therefore, that the low mean value for the Dakar African mothers' milks is apparent rather than real. It would be illuminating to know the corresponding mean value for European mothers resident in Dakar, using the method of determination employed by Auffret & Tanguy (1949); but such determinations apparently were not done.

SUMMARY

1. The reported deficiency of methionine in the breast milk of West African mothers appears to be of relevance in regard to (1) the hepatic fibrosis which occasionally occurs while infants are still exclusively breast fed, and (2) the high incidence of kwashiorkor at weaning time and thereafter. In South Africa kwashiorkor is common although it does not affect wholly breast-fed infants.

2. Determinations of methionine concentration in the breast milk of twenty-nine Bantu compared with twenty-five local South African European mothers revealed no abnormality in this respect, mean values obtained being 29·7 mg and 26·2 mg/100 ml. respectively.

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Food Preparations Used in Weaning Urban Bantu Infants

By A. R. P. WALKER, DOROTHY C. FLETCHER, EMMERENTIA S. P. STRYDOM and MARIANNE ANDERSSON

Human Biochemistry Unit of the South African Institute for Medical Research, Johannesburg and the South African Council for Scientific and Industrial Research

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In South Africa, it is customary for Bantu mothers to feed their babies almost exclusively at the breast for from 6 to 9 months, and subsequently to feed them partly at the breast for a variable period, sometimes as long as 3 years. In urban centres, in contrast with rural areas, the position differs somewhat, for Bantu women are often employed in domestic service or factories. When such women become mothers, they often want to return to work as soon as possible after parturition. Occasionally, therefore, their babies are cared for by relatives, so that premature weaning occurs.

As is well known, the most critical period in the nutritional life of the Bantu commences with weaning. The occurrence of the crisis is ascribed to ignorance, to the limited ability to buy milk products or nutritionally satisfactory milk-substitute foods, and to the fact that the weaned child is not given preferential treatment, but has to compete for the available food with the older members of the family group (Brock & Autret, 1952).

The commonness of undernutrition and malnutrition among Bantu children at weaning suggested to us that it would be of value to determine the composition of the food actually prepared by Bantu mothers for their children.

EXPERIMENTAL

Subjects and samples. In Johannesburg there are about half a million Bantu, of whom the majority dwell in townships south of the city. The region is served by Baragwanath Non-European Hospital which has 1350 beds. To obtain our main series of samples we took advantage of the fact that mothers seeking medical attention for themselves or their children usually prepare food to be given to the children while waiting in the out-patient department. The subjects whose feeds were sampled were selected at random, except that patients too ill to suck were not represented because their mothers had not brought food for them. Of this main series of subjects, twenty-four were under 6 months, thirteen were from 7 to 12 months, seven were from 13 to 18 months, and fourteen were from 19 to 24 months. Of the fifty-eight samples collected, fifty-three were from bottles; five samples of thicker consistency were taken from other containers such as pans or tins. From four to eight samples were collected on one morning each week.

A smaller series of nineteen samples was obtained by a municipal health visitor when calling at Bantu homes. Of the child consumers, seven were from 7 to 12 months,

and twelve from 13 to 18 months. Twelve of the samples were from bottles; the remaining seven, which were of thicker consistency, were taken from cooking pots.

The preparations given in feeding bottles were classified as:

Cereal paps, mainly of maize, prepared with or without some milk.

Proprietary foods containing cereals and dried milk, made up with or without milk.

Proprietary dried-milk products prepared with water only.

Miscellaneous mixtures.

The twelve samples given with a spoon were all thick cereal paps.

Methods. Total solids, ash, and protein were estimated by methods described by McCance & Shipp (1933) and McCance, Widdowson & Shackleton (1936). Fat was estimated by the Röse-Gottlieb method, with occasional checks by the method of Werner & Schmidt, both as outlined by Cox (1950).

RESULTS AND DISCUSSION

The results, which include mean values, with the standard deviation and range, for the percentage of the chief constituents in the foods analysed are set out in Table 1.

The samples collected at the out-patient department and in the homes were found to conform in their mean composition and range of constituents, so that the values for all the samples could be assembled in the same table. The uniformity of composition showed that the samples collected at Baragwanath Hospital could be taken as approximately representative of food prepared for the children at home.

The investigation showed that, in general, food mixtures were too much diluted. Except for the thick cereal paps given to the older children, the mixtures were almost invariably inadequate in calories, and the thin cereal paps, the proprietary cereal and dried-milk foods, and the miscellaneous foods were usually too low in protein concentration. These observations are in harmony with the fact that in Johannesburg more than half the patients in wards for children up to 2 years old are suffering from obvious malnutrition or undernutrition (Kahn, 1954).

Apart from poverty and ignorance we have come across another reason why food mixtures are too much diluted. A mixture prepared wholly or largely from cereal products and made up to fulfil calorie requirements is a gruel too thick to be consumed from a bottle. Bantu mothers face the difficulty by making the mixture too weak, by cooking it lightly to keep it thin, or by grossly enlarging the hole in the teat. Quite apart, therefore, from the nutritive inadequacy of a cereal-pap diet, it is virtually impossible for infants to make satisfactory progress on foods such as we have analysed.

The errors in preparation, which we have demonstrated, cannot, however, all be attributed to the ignorance or other failings of the Bantu mothers. We have obtained samples of all the types of commercial baby foods available in Johannesburg, and prepared feeds strictly according to the instructions on the label. We found that individual level tablespoons or other measures of powder differed in amount by as much as 10%. Corresponding differences when measuring water amounted to about 30%, and the amount of total solids varied by as much as 20%. Obviously, if such differences occur in preparations made in the laboratory, larger differences in mixtures made even by European mothers, let alone Bantu mothers, are only to be expected.

Table 1. *Average composition (a, value with standard deviation; b, range; c, number of samples analysed) of, and number of samples deficient in protein or calories in, food preparations for Bantu babies under 2 years of age*

Food preparation		Total solids (%)	Ash (%)	Protein* (%)	Fat (%)	Carbohydrate by difference (%)	Estimated calories (Cal./100 ml. fluid)	No. of samples deficient in protein on basis of 2·3 % recommended for artificial-milk mixtures (Clements, 1949) (%)	No. of samples deficient in calories on basis of 70 Cal./100 ml. breast milk (Clements, 1949) (%)
Thin cereal paps	(*a*)	9·7 ± 1·8	0·21 ± 0·14	0·8 ± 0·5	0·4 ± 0·1	8·3	40	100	100
	(*b*)	4·6–12·2	0·03–0·50	0·2–1·8	0·1–0·9				
	(*c*)	13	13	13	4				
Proprietary cereal dried milk mixtures	(*a*)	10·9 ± 4·1	0·43 ± 0·15	1·6 ± 0·8	0·7 ± 0·4	8·2	46	79	86
	(*b*)	4·5–20·0	0·22–0·71	0·6–4·5	0·07–3·2				
	(*c*)	14	14	14	11				
Dried-milk preparations	(*a*)	9·6 ± 4·0	0·50 ± 0·10	2·2 ± 1·2	2·1 ± 1·5	4·8	47	43	75
	(*b*)	3·9–16·0	0·21–0·70	0·4–7·2	0·7–6·0				
	(*c*)	12	12	12	12				
Miscellaneous mixtures	(*a*)	10·9 ± 3·1	0·32 ± 0·20	1·5 ± 1·0	1·4 ± 0·8	7·7	49	70	92
	(*b*)	6·0–14·1	0·06–0·60	0·2–2·9	0·2–3·6				
	(*c*)	26	26	25	26				
Thick cereal paps	(*a*)	18·6 ± 4·9	0·70 ± 0·22	2·5 ± 1·1	0·9 ± 0·3	14·5	76	33	25
	(*b*)	12·5–26·1	0·35–1·5	1·2–4·7	0·1–3·4				
	(*c*)	12	12	12	10				

* Factor for conversion of nitrogen into protein was for cereal paps 6·25, for dried-milk preparations 6·38, for all other mixtures 6·30.

In a recently published paper Hytten (1954) reported the analysis of 100 artificial-milk mixtures prepared by Aberdeen mothers for their babies; seventy-eight of the samples were found to be inadequate calorically. Among white children, serious errors in food preparation and consumption would in time be reflected in the child's clinical state, and before long medical advice would be sought. With the Bantu the position is different, for a nutritional set-back at weaning is taken almost for granted, and a child can become very ill before the regimen is changed or the child brought to hospital. In the excellent clinical studies of Dean (1953) with milk-substitute foods, the preparations given to the children were closely controlled. What we have been observing is the uncontrolled side. If the observations we have made on the Witwatersrand are representative of other similar areas, the outlook is depressing, for it would seem that no matter what excellent foods are made available, their effectiveness will be reduced, and their nutritive value remain suspect, until they are correctly prepared for consumption. It is disturbing also to realize that such a state of affairs obtains, in spite of the bulk of urban Bantu women being literate, and in spite of a most determined campaign of nutritional instruction by paediatricians, clinic medical officers, and health and social workers.

SUMMARY

1. Among the young children of urban South African Bantu, undernutrition and malnutrition are very common at and after weaning.

2. The diet of children under 2 years of age was studied. Fifty-eight samples of food were taken from the bottles or other containers brought by mothers for their children when waiting in the out-patient clinic of the Baragwanath Hospital in Johannesburg, and 191 samples were taken in the home in Johannesburg.

3. The food mixtures included cereal paps, proprietary mixtures of cereals and dried milk, and preparations of dried milk.

4. Samples of the foods were analysed for total solids, protein, fat and ash.

5. It was found that a great many of the samples were too highly diluted so that the concentration of protein and calories was so low that the child could not make satisfactory progress.

6. The numerous serious causes of over-dilution are discussed, and it is stressed that, even apart from them, the instructions given with commercial infant foods often permit the total solids in the liquid food to vary by as much as 30%.

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IMPAIRMENT OF SWEAT SECRETION IN MALNOURISHED INFANTS

By E. KAHN,* M. D. RAND, M.R.C.P.E., D.C.H. (R.C.P. & S.)
Johannesburg, South Africa
AND
A. R. P. WALKER,† PH.D.
Cape Town, South Africa

DURING hot summer weather African infants suffering from malnutrition tend to become feverish. The results of the investigations to be described indicate that in certain stages of malnutrition there is an impairment of sweat secretion, and that this defect may well cause fever in hot environments.

METHODS

The experiments were designed to compare under standard conditions of heat stress the sweat secretion and variations in body temperature of 13 severely malnourished infants and 15 controls.

The criterion for the selection of malnourished infants for these tests was the presence of nutritional oedema (Table 1A, Group 1). Other stigmata of infantile malnutrition (kwashiorkor) were also present, but they varied from case to case. Patients who were moribund or suffering from chronic illnesses in addition to malnutrition were excluded. In nine members of this group the exposure to heat stress was repeated some two to six weeks later, when the nutritional oedema had disappeared under dietetic treatment. Controls consisted of eight infants without clinical evidence of malnutrition (Group 2) and seven others who had recovered from malnutrition, but who had not been exposed to heat stress previously, and therefore had not become acclimatised to heat whilst oedematous (Group 3).

The three groups of children were subjected to atmospheric conditions simulating those existing in the poorer type of African dwelling in hot summer weather. Tests were conducted in an air-conditioned room during the winter months, to eliminate the factor of acclimatisation to heat which is unavoidable in summer. The room was heated to 80°F. before the start of the experiments. After the infants had been admitted, the temperature was raised to 90°F. in about 30 minutes, and was maintained at that level for one hour. The total period of exposure to heat stress thus extended over 1½ hours, and during this time the relative humidity of the air in the room varied between 40% and 45%. Up to six infants could be accommodated in the room at the same time. On each occasion one to three oedematous infants were observed together with normal controls and with infants who had recently recovered from malnutrition. All were dressed in thin cotton jackets and napkins; they were not covered by bed clothes.

The response of the sweat glands to this exposure to heat was determined quantitatively by a modification of the method used by Darling *et al.* (1953) when studying children suffering from fibrocystic disease of the pancreas: A previously dried piece of lint, 2″ x 3″ in size, was applied to the abdominal wall just above the umbilicus. The lint was covered with a slightly larger square of oiled silk (B.P.C.), the edges of which were sealed to the skin with adhesive tape. The sweat secreted in the area covered by the lint was measured by weighing the lint in the same rubber-stoppered bottle before and after a test. Body temperature was measured rectally with a clinical thermometer at the beginning and the end of tests.

An attempt was made to ascertain how far results would be affected by prolongation of thermal stress and by variations in the degree of oedema. To this end, another 13 infants were subjected to thermal stress for four hours, instead of the usual 1½ hours. Other experimental conditions remained the same as in previous tests. Six of these subjects suffered from varying degrees of nutritional oedema, four were well-nourished controls, and three were

* Senior Paediatrician, Baragwanath Hospital.
† Human Biochemistry Unit of the South African Institute for Medical Research, Johannesburg, and South African Council for Scientific and Industrial Research.

TABLE I

SWEAT SECRETION (MG. PER SIX SQUARE INCHES OF ABDOMINAL SKIN) AND BODY TEMPERATURES AT BEGINNING AND END OF EXPERIMENTS
(*Degrees Fahrenheit*)

A. Exposure to Heat Stress 1½ Hours

Group 1. Malnourished Infants		Group 2. Normal Controls	Group 3. Cases Recovered from Malnutrition But Not Previously Exposed to Heat Stress (Unacclimatised)
Oedematous	After Loss of Oedema		
53 mg. (98.0– 99.6°F.)	124 mg. (99.4– 98.8°F.)	167 mg. (97.0– 98.4°F.)	208 mg. (97.0– 98.4°F.)
46 mg. (99.4–102.0°F.)	345 mg. (97.0– 99.2°F.)	154 mg. (98.4– 99.6°F.)	724 mg. (98.0– 99.0°F.)
66 mg. (98.8– 99.6°F.)	551 mg. (99.2– 99.4°F.)	237 mg. (98.8–100.0°F.)	114 mg. (99.0–100.0°F.)
67 mg. (100.0–104.8°F.)	178 mg. (100.0–100.2°F.)	97 mg. (97.4– 99.2°F.)	128 mg. (100.2–100.0°F.)
64 mg. (99.6–101.2°F.)	Died	140 mg. (99.6– 99.0°F.)	137 mg. (98.6– 99.0°F.)
83 mg. (98.4– 99.6°F.)	237 mg. (97.4–100.4°F.)	224 mg. (98.0– 99.4°F.)	158 mg. (99.8–100.2°F.)
79 mg. (98.4– 99.8)°F.	197 mg. (99.6–100.1°F.)	115 mg. (99.0– 99.3°F.)	113 mg. (99.4–100.3°F.)
56 mg. (100.0–100.0°F.)	330 mg. (98.4– 99.6°F.)	113 mg. (100.0–100.0°F.)	
51 mg. (99.4–100.8°F.)	147 mg. (99.6– 99.6°F.)		
94 mg. (99.6–100.2°F.)	142 mg. (97.0–100.0°F.)		
67 mg. (99.2–100.0°F.)	—		
71 mg. (100.0–100.6°F.)	—		
68 mg. (98.4– 99.2°F.)	—		

B. Exposure to Heat Stress 4 Hours

64 mg. (96.6– 99.4°F.)	—	501 mg. (99.0–100.2°F.)	602 mg. (98.4–100.6°F.)
*199 mg. (98.4– 99.6°F.)	—	168 mg. (100.4–101.4°F.)	308 mg. (99.2–100.2°F.)
*277 mg. (100.8–101.2°F.)	—	317 mg. (99.4–100.6°F.)	450 mg. (100.8–104.0°F.)
*137 mg. (99.8–101.0°F.)	304 mg. (99.6–101.2°F.)	173 mg. (99.6–101.0°F.)	
*66 mg. (96.6–100.6°F.)	—		
*90 mg. (99.6–100.4°F.)	—		

* Oedema waning.

infants who had recently recovered from malnutrition (Table 1B).

RESULTS

Our results are summarized in the accompanying tables. It is apparent that: 1) Under the same environmental conditions, infants with nutritional oedema secreted less sweat than those in the control groups. (Table IA: Oedematous infants in Group 1 average 66 mg., range 46 to 94 mg., against combined control groups average, 188 mg., range 97 to 724 mg.) 2) They regained their ability to sweat freely, when their nutritional state improved. 3) There was no direct correlation between the extent of the oedema and the degree of impairment of sweat secretion of two infants with oedema comparable in extent who were exposed to heat stress for four hours, one secreted 66 mg. of sweat, whereas the other secreted 277 mg. (Table IB). 4) Clinical examination of the infants during the tests showed that the impairment of sweat secretion was not confined to the abdomen, but involved the whole body including axillae and groins. 5) During the tests, the rise in body temperature was higher in the oedematous infants (mean rise 1.46°F.) than in the normal controls or the infants who had recently recovered from malnutrition (mean rise in both groups combined 0.70°F.).

Comment

The above experiments show that infants suffering from severe malnutrition did not sweat freely when exposed to heat stress. No correlation was detected between the extent of the oedema and the severity of the impairment of sweat secretion. It is likely, therefore, that the dysfunction of the sweat glands was attributable to some aspect of malnutrition other than the oedema which had been our main criterion in the selection of the infants. The reduced sweat response of the oedematous children was not due to physical inactivity, because some members of the control groups perspired freely although they slept throughout the experiments.

On the average, body temperatures rose higher in the oedematous infants than in the other subjects. The difference between the mean rise in body temperature in the oedematous group (1.46°F.) and that in the combined control groups (0.70°F.) was 0.76°F. If this finding is subjected to statistical analysis by applying Fisher's *t*-test for significance of difference between means, it is found that the probability of this being a chance finding is between 1:10 and 1:20. Although this is not accepted as a highly probability value, it gains in significance by the fact that the same trend was observed in infants exposed to heat stress for four hours. Therefore, the greater temperature rise in the oedematous infants was probably not attributable to chance finding.

However, it was not possible to predict in individual cases how the body temperature would change under the influence of heat stress. This can be explained to some extent by differences in motor activity among children during the tests and by the relatively short time of exposure to thermal stress: all the oedematous infants were apathetic and hardly moved, whereas some of the other babies played in their cots with inexhaustible energy. Furthermore, under "natural" conditions African infants are exposed to more severe and prolonged heat stress than in the tests, because they are kept throughout the day on their mothers' backs wrapped in blankets, or in ill-ventilated rooms which are roofed with corrugated iron. Physiological considerations suggest that under such conditions differences in body temperatures between normal infants and those with impaired sweat secretion may be more pronounced than in our experiments.

The cause of the impairment of sweat secretion in severe untreated malnutrition is unknown. A similar defect exists in patients suffering from congestive cardiac failure. These cases have raised body temperatures during hot summer weather (Cohn and Steele, 1934) which have been attributed to an impaired sweat secretion (Burch, 1946). The response of the sweat glands returns to normal when cardiac function improves under treatment. It is thought that the dysfunction of the sweat glands during congestive heart failure is caused, not by cardiac oedema, but by an impairment of the peripheral circulation (Burch, 1953).

Infantile malnutrition (kwashiorkor) is not associated with congestive cardiac failure; but there is evidence that the peripheral circulation is markedly reduced by vasoconstriction (Utheim, 1920; Marriott, 1920). Our observations over several years have shown that this reduction occasionally assumes such proportions that the tips of the fingers, toes or ears undergo spontaneous gangrene. It is, therefore, suggested that the depression in the function of the sweat glands in infantile malnutrition may well depend on a poor peripheral circulation.

Further work on this subject is proceeding.

Summary

Severely malnourished African infants are often feverish during hot summer weather. To elucidate the cause of this phenomenon, malnourished infants and controls were studied under standard conditions of heat stress with regard to sweat secretion and rise of body temperature. There was a

marked impairment in the function of the sweat glands in the malnourished infants and the mean body temperature rose higher than that of the controls. The derangement of the sweat secretion was not related to the extent of the nutritional oedema. There was no close correlation between impairment of sweat secretion and rise in body temperature. The possible reasons for these observations are discussed. It is suggested that dysfunction of the sweat glands in severe malnutrition is caused by a poor peripheral circulation.

We wish to acknowledge the technical help of Miss U. B. Arvidson during the early stages of this work, and to thank Dr. A. M. Adelstein for the statistical evaluation of the data.

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Disminución de la Secreción del Sudor en Niños Africanos Desnutridos

Habiéndose observado que niños desnutridos africanos presentaban fiebre durante las épocas calurosas, los autores trataron de investigar la causa del fenómeno habiendo encontrado como resultado de su estudio disminución de la secreción sudoral en algunas etapas de la desnutrición por lo que creen que este defecto puede ser la causa de la fiebre en las épocas calurosas.

Los estudios se hicieron comparativamente entre 13 niños muy desnutridos y 15 niños control bajo condiciones semejantes de esfuerzo ante el calor. Todos los niños desnutridos eran edematosos; dos a seis semanas después de la primera experiencia, se repitió al haber desaparecido el edema con un tratamiento dietético. Los niños control formaron dos grupos: uno de 8 niños en buen estado nutricional (grupo 2) y 7 recuperados de desnutrición que no habían sido expuestos al calor previamente (grupo 3). A los tres grupos se les sujetó a condiciones atmosféricas semejantes a las existentes durante las épocas calurosas en las habitaciones africanas más pobres. La respuesta de las glándulas sudoríparas durante el experimento se determinó cuantitativamente por el método, ligeramente modificado, que han usado Darling y colaboradores en niños con enfermedad fibroquística del páncreas.

Los resultados observados fueron: secreción sudoral inferior en los niños edematosos desnutridos que en los niños control, con recuperación de la capacidad de sudar libremente tan pronto como mejoraban de sus condiciones nutricionales; no se encontró relación directa entre la extensión del edema y el grado de disminución de la secreción de sudor ni tampoco que este fenómeno se localizara exclusivamente al abdomen, ya que abarcó también todo el cuerpo incluyendo axilas e ingles; por último, se observó un aumento mayor de temperatura corporal en los niños edematosos que en los niños control de ambos grupos.

Puesto que no se encontró correlación entre el edema y el grado de disminución de la secreción sudoral, la disfunción de las glándulas se atribuyó a algún otro aspecto de la desnutrición aparte del edema. No se pudo predecir en los casos edematosos el cambio individual de la temperatura corporal bajo la influencia del calor, explicable quizá por las diferencias en actividad motora entre los niños durante las experiencias.

Se desconoce la causa de la disminución de la secreción sudoral en los niños desnutridos no tratados, pero los autores suponen, a semejanza de lo observado en pacientes con insuficiencia cardiaca, que la depresión funcional de las glándulas sudoríparas depende de una pobre circulación periférica.

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An investigation of the rarity of infantile scurvy among the South African Bantu

BY MARIANNE ANDERSSON AND A. R. P. WALKER

Human Biochemistry Research Unit of the South African Institute for Medical Research, Johannesburg, and the South African Council for Scientific and Industrial Research

AND H. C. FALCKE

Department of Paediatrics, Coronation Non-European Hospital, Johannesburg

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Various nutritional problems of Bantu infants and young children have been investigated recently at this centre. We have studied, for example, the composition of breast milk (Walker, Arvidsson & Draper, 1954) and of the foods used at weaning (Walker, Fletcher, Strydom & Andersson, 1955), the utilization of nutrients by infants during and after gross malnutrition (Walker, Kahn & Reynolds, 1955) and so forth. One point which has particularly impressed us is that, though in all other respects the various stigmata of malnutrition and undernutrition are such as would be expected from the inadequate diet, infantile scurvy does not apparently occur. Thus, in Johannesburg, at Baragwanath Non-European Hospital (1350 beds), out of about 6000 admissions under 2 years of age during the last 5 years, there have been only two cases of frank infantile scurvy. At Coronation Hospital (500 beds) within the last 5-year period, there have been only two cases of the disease among over 3000 admissions under 2 years of age.

With breast feeding, particularly when practised for protracted periods as in rural areas in Africa, there is no doubt that the amount of vitamin C from the milk and from the irregular amounts of fruit and vegetables provided, is sufficient to protect against the development of infantile scurvy. In urban areas, however, breast feeding is practised for shorter periods, indeed, some mothers, in their desire to get back to work quickly, wean their babies as soon as possible after parturition. In such areas, the giving of fruit and vegetables is obviously limited, and it is generally accepted as being by no means uncommon for infants to be weaned on an almost exclusive diet of cereal 'paps' or similar foods, likely to contain either very little or no vitamin C. Under conditions where infantile scurvy would be expected to occur frequently, and occasionally severely, available evidence indicates the disease to be virtually absent. Freedom from the disease cannot be ascribed to racial differences: firstly, the disease occurs among American Negro (Hess, 1920) and also Indian (Singh, 1954) infants; secondly, scurvy occurs among Bantu adults (Bronte-Stewart, 1953; Grusin & Kincaid-Smith, 1954).

In an endeavour to throw light on the subject, we have carried out an investigation on (1) Bantu infants under the age of 2 admitted to Coronation Hospital suffering

from severe malnutrition, and (2) Bantu infants seen in the out-patients' department. Studies have included clinical and radiological observations, also determinations of the vitamin C concentration in the plasma of the subjects examined, and in popular baby foods prepared by Bantu mothers.

EXPERIMENTAL

Subjects

Malnourished children in hospital. The thirty-three children investigated in hospital were urban Bantu infants of ages ranging from 4 to 24 months, the mean age being 11 months. Sixteen were severely malnourished, as shown by retarded growth, dyspigmentation of the skin and often of the hair, and occasionally by dermatosis and oedema. Four had gastro-enteritis, seven suffered from various infections; the remaining six had miscellaneous complaints. An X-ray examination of the femur was carried out for each child.

'Normal' Bantu infants. Twenty-nine were selected from the out-patients' department, having been brought there mainly for minor complaints or for a routine check. Their ages ranged from 4 to 18 months, the mean age being 10 months.

Diet

The malnourished subjects were receiving no breast milk. Of the twenty-nine out-patient subjects, sixteen were wholly or partly breast fed; the remaining thirteen were having either very little or no breast milk. Only one patient, a malnourished subject, was said to receive fruit or vegetables regularly. The mothers of all the other infants said that such foodstuffs were given infrequently or not at all. The almost exclusive sources of nourishment were stated to be: (1) cereal 'paps' prepared with or without a little milk, (2) proprietary cereal–dried-milk mixtures prepared usually with water only, (3) dried-milk mixtures made up with water, and (4) miscellaneous mixtures (see Walker, Fletcher *et al.* 1955).

Samples of foodstuffs for vitamin C determination were collected from preparations brought by mothers for feeding their babies while waiting at the out-patients' department. A previous investigation (Walker, Fletcher *et al.* 1955) has revealed that such samples are representative of what urban Bantu mothers prepare at home for their young children.

Methods

In the plasma, the vitamin C present is usually regarded as being in transport to the erythrocytes, white cells and platelets (Bicknell & Prescott, 1953). Plasma vitamin C is thus the most labile of fractions present in the components of the blood, and in general reflects recent intake of the substance. Since the rarity of scurvy in Bantu infants is well recognized, it was thought that a verification of this belief might be best achieved by showing that a low plasma concentration of vitamin C (consistent with a scorbutic state) was virtually absent in the series of subjects examined, whether malnourished or well. Accordingly, we have limited our studies to determining

vitamin C concentrations in the plasma rather than in whole bood or 'buffy' layer. To determine the plasma value, 4 ml. blood were collected from the external jugular vein or from the femoral vein, usually about 3 h after breakfast. The blood was preserved with one drop of 30% (w/v) potassium oxalate. In the first few determinations, two drops of 5% (w/v) potassium cyanide were added, as recommended by Pijoan & Klemperer (1937), but this procedure was found unnecessary when determinations were carried out within an hour of collection. Vitamin C was determined by the method described by King (1947). The vitamin concentration in food mixtures was determined by the method described by Kon & Mawson (1950).

RESULTS

Results for the vitamin C concentrations in the blood plasma and in the infant foods are given in Tables 1 and 2.

Radiological observations of the end of the femur showed no stigmata of scurvy; for example there was no evidence of the 'white line' (Bicknell & Prescott, 1953; Graham, 1952).

Table 1. *Vitamin C concentration in the plasma of the urban Bantu infants, and values for American infants (Snelling, 1939)*

Group of subjects	No. of subjects	Vitamin C (mg/100 ml. plasma) Mean	Range
Infants in hospital			
All infants	33	0·36 ± 0·18*	0·17–0·97
Severely malnourished	16	0·26	0·20–0·41
With gastro-enteritis	4	0·42	0·17–0·94
With various infections	7	0·53	0·36–0·80
With miscellaneous ailments	6	0·41	0·25–0·60
Infants attending the outpatients' department			
All infants	29	0·63 ± 0·33*	0·17–1·41
Breast-fed	16	0·80	0·35–1·41
Artificially fed	13	0·42	0·17–1·03
American infants†			
Breast-fed	31	0·76	0·05–1·70
Artificially fed	127	0·23	0·08–1·58

* Mean value with standard deviation.

† Among the thirty-one breast-fed infants eight were receiving orange supplements, but it was stated that there was no essential difference between groups with and without such supplementation. Among the artificially fed, seventy-nine infants given orange juice had a mean plasma concentration of 0·30 mg vitamin C, and forty-five with no orange juice of 0·12 mg vitamin C/100 ml. plasma.

Table 2. *Vitamin C concentration in the food preparations given to urban Bantu infants*

Type of food preparation	No. of samples	Vitamin C (mg/100 ml. mixture) Mean	Range
Cereal 'paps'	10	0·22	0–0·66
Proprietary cereal—dried-milk mixtures	6	0·11	0–0·22
Dried-milk mixtures	6	0·29	0–0·69
Miscellaneous mixtures	6	0·43	0–0·93

DISCUSSION

The clinical picture of infantile scurvy is well known (Hess, 1920; Bicknell & Prescott, 1953; Graham, 1952). In no Bantu infant examined was there evidence of this disease. The possible presence of subclinical scurvy, however, could not be excluded.

Table 1 indicates, firstly, that the values for plasma vitamin C in the sick subjects were compatible with an absence of frank scurvy, and secondly, that the values in the out-patient infants were similar to those given for American subjects (Snelling, 1939). The lower mean value for the infants in hospital is presumably related to the prevalence of infections among them: twelve of the group of sixteen severely malnourished infants were suffering from gastro-intestinal disorders.

The source of the vitamin is puzzling. Its concentration in the baby foods examined was very low (Table 2). If, as we think often happens, babies are weaned exclusively on such foods, then their maximum daily intake can scarcely exceed a few milligrammes. Of the twenty-eight samples of foodstuffs examined, twelve contained no vitamin C; from the information obtained it has been calculated that of the sixteen remaining samples eleven provided a daily intake of less than 3 mg; the other five samples provided from 4 to 8 mg daily. Undoubtedly a large proportion of urban Bantu infants receive some vitamin C from fruit and vegetable sources, although all observations and inquiries made testify the irregularity of the practice. If such supplementation is the reason why scurvy among weaned or partly weaned Bantu infants is almost unknown, the implication is that all subjects examined by us, indeed, all such Bantu infants in general, are receiving supplements, which is highly improbable. Yet, the only alternative is to postulate an endogenous production of the vitamin. Further investigations to elucidate the problem are being undertaken.

SUMMARY

1. Thirty-three urban Bantu infants with severe malnutrition or other ailments necessitating hospital treatment and twenty-nine 'normal' infants attending the out-patients' department, all under 2 years of age, were examined in Johannesburg for clinical or radiological evidence of scurvy. Their plasma vitamin C concentration and the vitamin C content of the foods given to the weaned or partly weaned infants were determined.

2. No evidence of scurvy was found, and in all subjects the plasma vitamin C concentration was consistent with the absence of the disease, although the foods given to the infants contained very little vitamin C.

3. It is submitted that the possibility of endogenous production of the vitamin cannot be excluded.

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PARATHYROID FUNCTION IN VITAMIN D DEFICIENCY RICKETS

I. Phosphorus Excretion Index in Vitamin D Deficiency Rickets in South African Bantu Infants

L. S. Taitz, M.B., Ch.B., B.Sc., and C. D. de Lacy

The Department of Paediatrics, Baragwanath Non-European Hospital, Johannesburg; and Human Biochemistry Research Unit, Council for Scientific and Industrial Research, and South African Institute for Medical Research, Johannesburg, South Africa

FOLLOWING early observations of Erdheim[1] and Pappenheimer and Minor[2] that the parathyroid glands are hypertrophied in children dying with vitamin D deficiency rickets, it was postulated that secondary hyperparathyroidism plays a part in the pathogenesis of the bone and biochemical changes of this disease. In both rickets and hyperparathyroidism there is depression of inorganic phosphorus levels in plasma, elevation of alkaline phosphatase in serum, and bone demineralization, suggesting that the two diseases have similar pathophysiological mechanisms. The thesis that the biochemical abnormalities found in simple rickets are due to overaction of the parathyroid glands has received strong support from Albright and his colleagues.[3] Much evidence, largely indirect or circumstantial, has accumulated supporting this view. The feeding of rachitogenic diets to experimental animals has been shown to produce parathyroid hyperplasia,[4] while enlargement of these glands has been reported in patients with uremia associated with bone demineralization.

Several workers have demonstrated that patients with osteomalacia secondary to the malabsorption syndrome have increased renal clearance of phosphate.[5] This has been accepted as presumptive evidence of parathyroid overactivity, and it has been argued by analogy that the same response may occur in infantile rickets.[6]

There are, however, certain important differences between adult osteomalacia and childhood rickets. Comparatively, the latter is a much simpler metabolic defect resulting from an isolated deficiency of vitamin D, whereas the adult disease in the western world is usually a complication of a severe metabolic disorder such as uremia or steatorrhea, and is associated with many complicating biochemical abnormalities. Furthermore, the infant is a rapidly growing organism with progressive increase of total body calcium, whereas the adult metabolism is geared merely to the maintenance and repair of a static bone mass and the replacement of a small obligatory calcium loss in the stools and urine.

The present study was undertaken in view of the paucity of direct evidence of parathyroid over-activity in infantile rickets. The method chosen for the assessment of phosphate clearance is the phosphorus excretion index (PEI) of Nordin and Fraser.[5] This value is a function of the capacity of the renal tubule to re-absorb phosphorus and therefore, indirectly, of parathyroid activity. It is based on the traditional device of relating the renal clearance of phospho-

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The data presented in this paper form part of a thesis to be presented for the degree of Doctor of Medicine at the University of the Witwatersrand, Johannesburg.

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ADDRESS: (L.S.T.) 1106 Von Brandis Heights, Petersen Street, Hillbrow, Johannesburg, South Africa.

rus to the glomerular filtration rate expressed as the clearance of endogenous creatinine. The PEI has an important advantage over data from other methods in that the value is corrected for the actual level of the inorganic phosphorus in plasma by means of an equation derived from studies on normal subjects. A further advantage, of particular importance in small children, is the fact that accurate measurements of urine volume and minute output are not required. In addition, calcium infusion tests were undertaken in order to define the nature of the renal tubular reabsorption of phosphate in these patients, and its dependence on parathyroid activity.

The metabolic data presented in this paper provide evidence that secondary hyperparathyroidism may play a fundamental role in the patho-physiological adjustment to vitamin D deficiency.

MATERIAL AND METHODS

Forty-three urban South African Bantu children, aged 4 months to 2 years, were studied. Patients were selected on the basis of clinical evidence of rickets. The criteria adopted were the presence of craniotabes, rachitic rosary, and expansion of the distal metaphyses of the forearm. All children showed radiologic evidence of rickets, while the blood urea concentration and routine urinalysis were normal in each patient. In seven patients radiologic examination showed evidence of commencing healing.

The "normal" or control group consisted of eight infants who had normal weight for their age and showed no stigmata of malnutrition or clinical, radiologic, or biochemical evidence of rickets.

The following investigations were carried out on the patients and the normal controls.

Determination of the phosphorus excretion index (PEI) was carried out according to the method of Nordin and Fraser,[8] modified in certain respects because of the ages of the subjects and consequent difficulty in urine collection. These modifications are as follows. In female children, urine samples were obtained by catheterization of the bladder, while in males, Pauls' tubing was attached to the penis with adhesive tape. Collection periods varied between 2 and 7 hours, depending on the rate at which urine was voided. Blood specimens were always obtained at about the midpoint of the collection period. The phosphorus and creatinine concentrations in plasma and urine were determined according to the methods described by King and Wootton.[10]. This phosphorus-creatinine clearance ratio was calculated from the formula:

$$\frac{Cp}{Ccr} = \frac{Pcr \times Up}{Pp \times Ucr},$$

where C = renal clearance, p = inorganic phosphorus, cr = creatinine concentration, U = urine, and P = plasma.

The theoretical phosphorus-creatinine clearance ratio was calculated from the formula:

$$\text{Calculated}\frac{Cp}{Ccr} = Pp \times 0.055 - 0.07$$

By subtracting this figure from the actual ratio, the PEI was obtained. The theoretical (calculated) value is derived from values obtained from normal individuals subjected to varying plasma phosphate concentrations, and represents a regression line obtained from these data.

Calcium infusion tests were performed on five patients with florid rickets according to the method of Nordin and Fraser.[10]

In order to test the effects of high and low calcium and phosphorus intakes, 20 of the patients with florid rickets and the 8 control subjects were given standard milk feedings, while the remaining 16 patients with florid rickets and the 7 patients with healing rickets were given 0.2% saline in dextrose water for 24 hours prior to the performance of the PEI.

Alkaline phosphatase and calcium in serum were determined according to methods described by King and Wootton[7] and Langendorff[8] respectively.

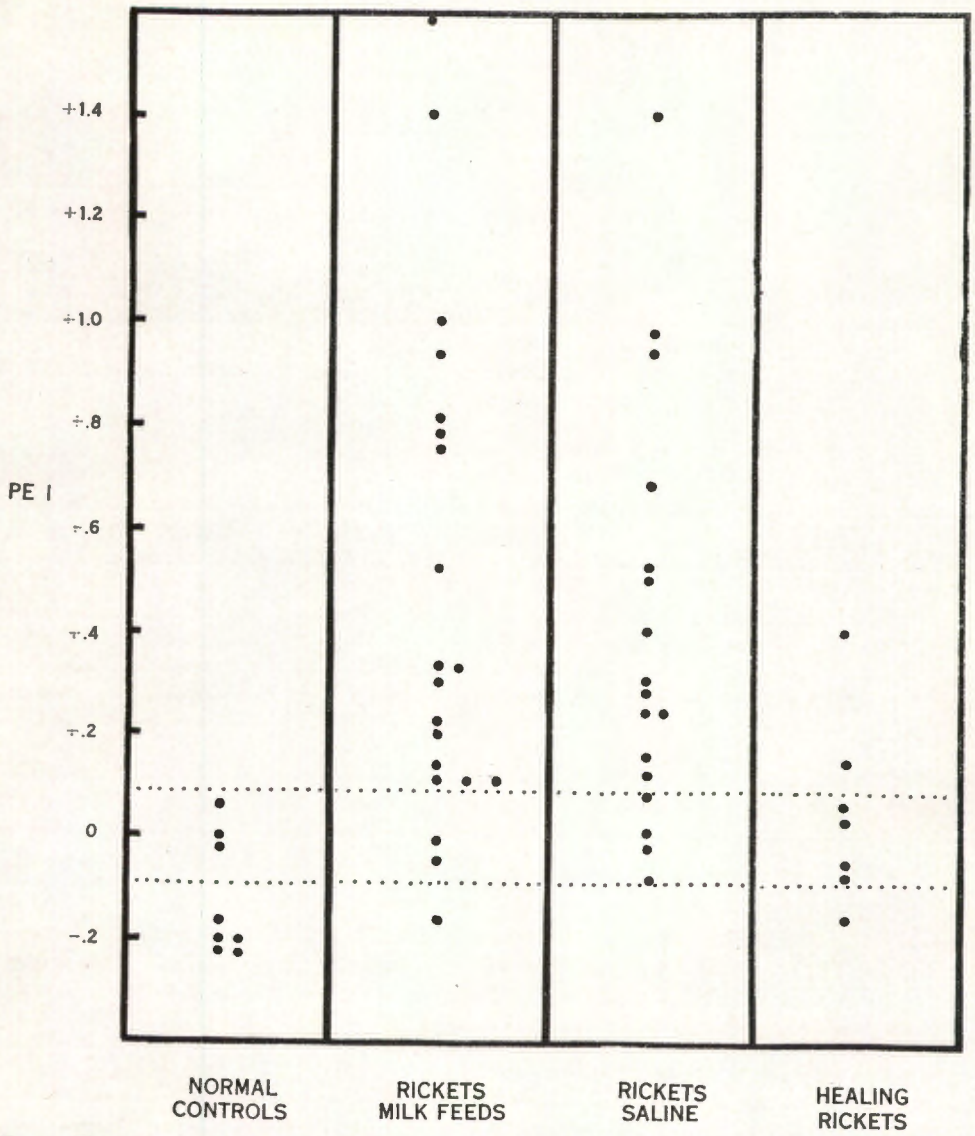

FIG. 1. The phosphorus excretion index in normal Bantu infants, infants with active rickets while receiving milk or dextrose-saline feedings, and infants with healing rickets. Dotted lines represent normal range in adult white subjects.

All patients were again x-rayed after one month's treatment with 5,000 units of vitamin D daily to determine whether the rickets was responding to normal therapeutic doses of the vitamin.

RESULTS

The PEI values of the patients in the different groups are shown in Figure 1. Subjects with active rickets showed a range of −0.16 to +1.6 with a mean of +0.41, whereas the normal control group varied between −0.22 and +0.04 with a mean of −0.125. Since only 6 of 37 subjects with active rickets had values falling within the normal range, these values are obviously significantly higher than those of the normal group. The patients with healing rickets showed a range of −0.18 to +0.4, with a mean of +0.034, which is significantly lower than in the active group but significantly higher than in the control group

TABLE I

RESULTS OF CALCIUM INFUSION TESTS IN FIVE CHILDREN WITH SIMPLE RICKETS

		Infusion				
Hours	*Findings**	*1*	*2*	*3*	*4*	*5*
2	PEI	+0.6	+0.52	+0.82	+0.91	+0.37
	Ca	8.4	8.0	9.4	8.0	8.3
	P	2.7	2.7	4.3	3.1	5.4
	GFR	..	..	..	67	61
4†	..	..	..	..	..	..
6†	PEI	+0.10	+0.40	+0.24	+0.38	+0.16
	Ca	9.4	9.4	11.6	9.4	10.2
	P	2.9	2.8	5.2	3.1	6.3
	GFR	..	..	..	73	64
8	PEI	+0.20	+0.23	+0.40	+0.02	+0.03
10	PEI	+0.12	..	..	..	..
12	PEI	+0.24	+0.34	+0.50	+0.28	+0.28
14	PEI	+0.50	+0.49	+0.78	+0.41	+0.40
16	..	..	..	..	..	..
18	PEI	+0.48	+0.48	−0.83	+0.56	+0.33
20	..	..	..	..	..	..
22	PEI	+0.50	..	..	+0.70	+0.31
24	PEI	+0.49	+0.49	+0.80	+0.65	+0.30
	Ca	8.7	9.3	9.6	8.0	8.0
	P	2.7	2.8	4.2	3.3	6.6
	Ca Inf	15	20	20	20	25

* PEI = phosphorus excretion index; Ca = calcium in serum (meq/liter); P = phosphorus in plasma (mg/100 ml); GFR = glomerular filtration rate (ml/min/M²); Ca Inf = calcium infused (mg/kg).

† Period of infusion.

(t test; $p < 0.05$).[12] There is no significant difference between the subjects given milk feedings as compared with those given saline ($p < 0.4 > 0.3$).

Calcium levels in serum in the rachitic children ranged from 2.5 to 4.8 meq/liter, with a mean of 3.5 meq/liter, whereas the control subjects had calcium levels ranging from 4.2 to 4.8 meq/liter, with a mean of 4.5 meq/liter.

The alkaline phosphatase level was above 25 King-Armstrong units in all but three of the subjects with active rickets, below 25 King-Armstrong units in all except one subject with healing rickets, and in all the control subjects.

The relationship between the inorganic phosphorus in plasma and PEI is illustrated in Figure 2. Patients with phosphorus levels exceeding 3.5 mg/100 ml had a significantly lower PEI than patients with phosphorus levels below 3.5 mg/100 ml ($p < 0.001$).

Figure 3 demonstrates the relationship between the alkaline phosphatase and the PEI (correlation co-efficient $r = 0.44$; significant at 5%).

The results of the calcium infusion tests are demonstrated in Table I. In each patient there is depression of the PEI, with elevation or no change of the plasma phosphorus, followed by a return to near previous levels within 24 hours.

COMMENT

It is clear from these observations that infants with active rickets have marked impairment of their ability to re-absorb phosphorus when compared with normal controls. Previous workers have assumed that a tendency to phosphorus diuresis is a manifestation of hyperparathyroidism,[10] but it has been pointed out[11] that increased phosphate clearance is a nonspecific response which reflects merely an altered maximal tubular re-absorption (Tm_p) for phosphorus which may be caused by a number of metabolic disorders such as Cushing's disease, the renal tubular disorders, myxedema, cirrhosis of the liver, and renal calculi. All these possibilities have been excluded in our choice of subjects.

The use of the PEI as a function of parathyroid activity has been criticised because some workers have found that the PEI may be normal in certain subjects with hyperparathyroidism.[12] These false-negative results do not appear to occur frequently enough to invalidate the type of statistical study that we have undertaken.

It cannot be completely excluded that the phosphate diuresis demonstrated may be due specifically to the effect of vitamin D deficiency on the renal tubule. It is well known that amino-aciduria is commonly present in children with vitamin D deficiency rickets and that is disappears when small doses of vitamin D are administered. It would not be surprising if an inability to re-absorb phosphate were another manifestation of the effect of vitamin D deficiency. This problem cannot be discussed without a brief allusion to the long-standing controversy regarding the action of vitamin D on the renal tubule.

The classic view that vitamin D causes a phosphate diuresis was advocated by Albright and his colleagues,[3] who believed that this effect was usually masked by the increased calcium absorption from the intestine and resulting suppression of parathyroid activity. Harrison, on the other hand, considered that vitamin D caused phosphate retention,[13] while Nicolayson and Eeg-Larsen[14] recently stated that there is no convincing evidence that the vitamin has any renal action at all.

The results of the calcium infusions tests in our patients throw some light on this problem, since they show an unequivocal fall in urinary phosphate clearance when calcium is administered intravenously. This fall is not due to depression of glomerular filtration rate (clearance of endogenous creatinine) which remained unaltered in two patients in which it was measured. Furthermore, the data have been expressed as a ratio of phosphorus to creatinine clearance, which would be unchanged were a fall in glomerular filtration rate the only factor involved. It may thus be concluded that the findings indicate that intravenous calcium increases the tubular reabsorption of phosphate in rachitic infants. This conclusion is identical with the observation of Nordin and Fraser[10] in subjects with osteomalacia and in normal subjects, and those of Ko and Fellers[15] in children with familial hyperphosphataemic rickets. The exact significance of these observations is not quite clear but there are good theoretical grounds for explaining them on the basis of parathyroid depression, since the principal controlling factor in the secretion of parathyroid hormone is the level of serum calcium. In addition, there is both radiologic and histologic evidence that parathyroid overactivity occurs in both osteomalacia and familial hypophosphataemic rickets.[15,18] It is therefore concluded that phosphate clearance in simple rickets is not independent of parathyroid control. Furthermore, the magnitude of the fall in PEI which we have demonstrated (in some cases reverting toward normal) suggests that the elevation of phosphate clearance is largely the result

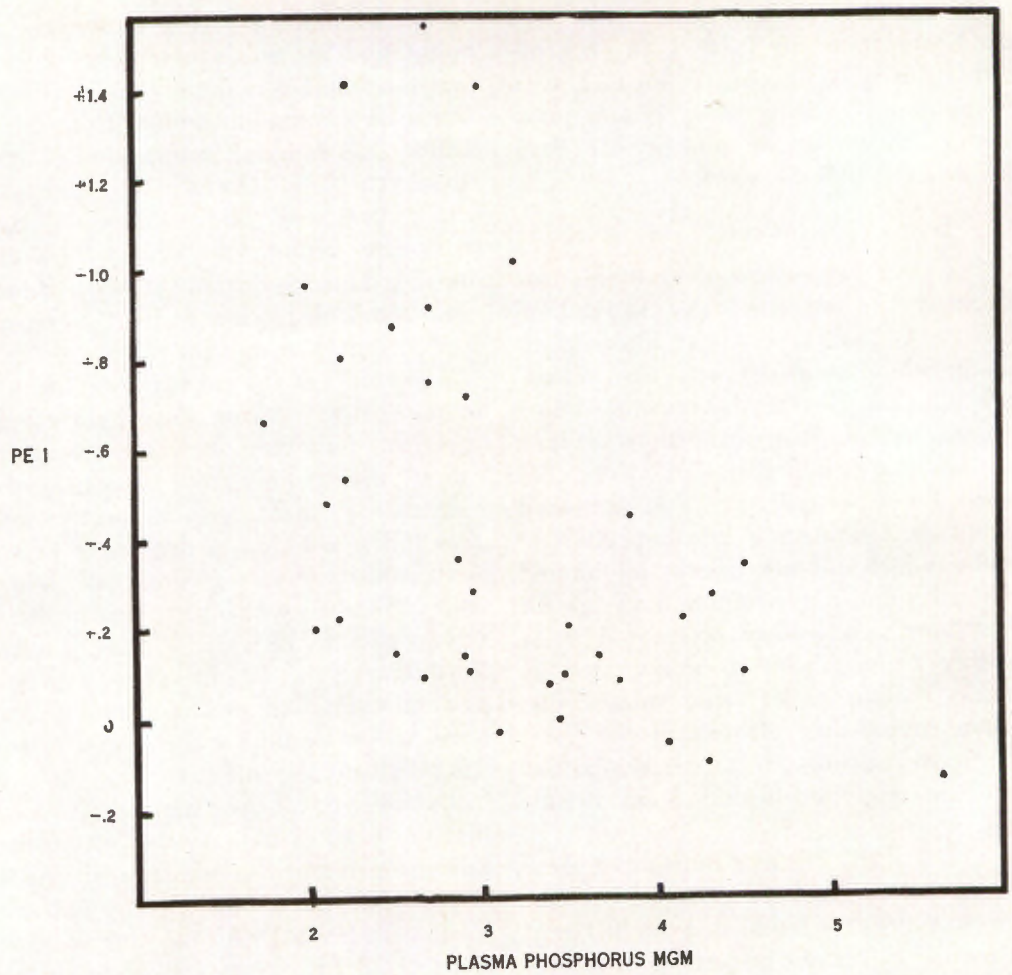

FIG. 2. Relation of phosphorus excretion index to plasma phosphorus in infants with active rickets.

of parathyroid overaction, while not excluding a contributory rôle to other factors such as vitamin D deficiency.

Considerable difficulty was experienced in attempting to achieve marked elevation of the serum calcium level despite the fact that doses of intravenous calcium far in excess of those recommended by Nordin and Fraser[10] (15 mg/kg) were used in several of the patients.

We are not able to explain the reason for this, but several factors have been considered, including the ages of the subjects (all less than 7 months of age) and the extreme severity of their bone disease. It is possible that the bones of these young and grossly rachitic infants may have a tremendous capacity for removing calcium from the blood.

Despite the modest elevation of serum calcium attained, the response of the phosphate clearance appears clearcut, indicating how sensitive the parathyroid-renal axis may be in these patients.

Two further points of interest arise. First, there is the relationship which has been demonstrated between the PEI and plasma inorganic phosphorus. The inverse correlation suggests that there is an important causal relationship between these factors. Indeed, it seems likely that secondary hyperparathyroidism is the main mechanism responsible for the hypophosphataemia and bone changes of vitamin D deficiency rick-

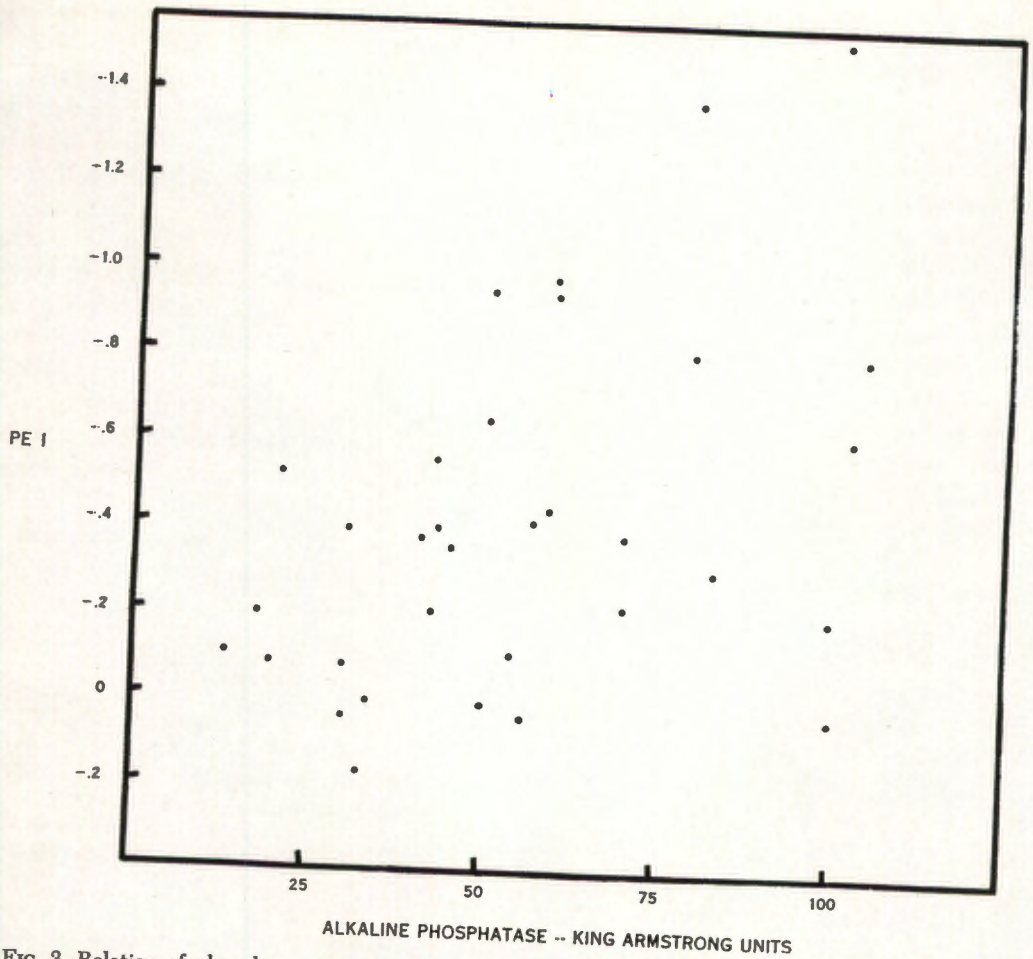

FIG. 3. Relation of phosphorus excretion index to alkaline phosphatase in infants with active rickets.

ets. Secondly, it is obvious that over-action of the parathyroids occurs in the majority of patients with rickets. Several recent publications do not stress the importance of this phenomenon and give the impression that it is comparatively infrequent.[16,17]

Assuming that hyperparathyroidism is the main mechanism of the decalcification which occurs in rickets and osteomalacia, it remains to be explained why the radiologic and histologic findings in these diseases differ from those of primary hyperparathyroidism. The possible explanation of these findings is based on the current view that parathyroid hormone exerts two separate effects, one on bone and the other on the kidney.[19]

In rickets the major effect of parathyroid overaction is to lower the phosphorus level in plasma since its secretion is kept in check by the increase in the calcium level resulting from the direct bone action. This results in hypophosphataemia and a fall in the calcium-×-phosphorus-solubility (activity) product. If this product falls below 30, calcium triphosphate cannot be incorporated in the hydroxyapatite bone crystals.[17,18] This in turn leads to the formation of uncalcified osteoid and the stimulation of osteoblast activity and excess matrix formation, thus producing the characteristic histologic features of osteomalacia.

In primary hyperparathyroidism the bone action is dominant, presumably because the parathyroids have become independent of

the serum control mechanisms. There is thus progressive bone erosion, osteoclast stimulation, and fibrosis resulting in osteitis fibrosa cystica. Clearly mixed pictures may occur, particularly in long-standing cases of malabsorption osteomalacia, while children with very severe vitamin deficiency rickets or "tubular" rickets show subperiosteal bone resorption characteristic of osteitis fibrosa cystica.[20]

A surprising finding in the study has been the wide range of the alkaline phosphatase-values and the broad scatter present when they are correlated with the PEI (Fig. 3). These findings suggest that other factors may also play a part in the elevation of the alkaline phosphatase that occurs in rickets. Nevertheless some correlation has been demonstrated between the alkaline phosphatase and the PEI. Discussion of this aspect, together with an analysis of the PEI in relation to calcium levels in serum, is the subject of a further contribution.

Finally, it must be pointed out that the PEI levels in the control group in this series (range -0.22 to $+0.04$) differ significantly from those of Nordin and Fraser,[5] whose 53 subjects showed a mean of 0 ± 0.09 ($p < 0.05$). This discrepancy may be explained in two ways. An unlikely possibility is that the observation is a racial variant in the South African Bantu child. A second and more plausible possibility is that children have a relative hypoparathyroidism when compared with adults, since eight adult Bantu had PEI levels within the normal range of Nordin and Fraser. The rapid incorporation of calcium in the growing bone of infants, together with the fact that they tend to have plasma phosphorus levels which are about 2 mg/100 ml higher than in adults, supports this view. A possible explanation of this finding may be that the higher calcium intake of children may lead to suppression of the parathyroid glands.

SUMMARY

A study of South African Bantu infants with vitamin D deficiency rickets revealed marked elevation of the phosphorus excretion index (PEI) as measured by the method of Nordin and Fraser. This finding is interpreted as evidence of secondary hyperparathyroidism, since the PEI was depressed by intravenous calcium infusion. In view of the inverse relationship demonstrated between phosphorus excretion and the plasma phosphorus levels in these children, it is suggested that secondary hyperparathyroidism may play a fundamental role in the evolution of the biochemical findings in this disease. An hypothesis is put forward to explain the histologic differences between rickets and primary hyperparathyroidism on the basis of the double action of parathyroid hormone. The PEI is a suitable technique for investigation of problems of calcium-phosphorus metabolism in childhood.

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PARATHYROID FUNCTION IN VITAMIN D DEFICIENCY RICKETS. II. THE RELATIONSHIP OF PARATHYROID FUNCTION TO BONE CHANGES AND INCIDENCE OF TETANY IN VITAMIN D DEFICIENCY RICKETS IN SOUTH AFRICAN BANTU INFANTS

BY

L. S. TAITZ, M.B., CH.B., B.SC., AND C. D. DE LACY

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PARATHYROID FUNCTION IN VITAMIN D DEFICIENCY RICKETS

II. The Relationship of Parathyroid Function to Bone Changes and Incidence of Tetany in Vitamin D Deficiency Rickets in South African Bantu Infants

L. S. Taitz, M.B., Ch.B., B.Sc., and C. D. de Lacy

The Department of Pediatrics, Baragwanath Non-European Hospital, and the Human Biochemistry Research Unit, South African Institute for Medical Research, Johannesburg

SEVERAL WORKERS have drawn attention to the varying biochemical patterns in patients with rickets and osteomalacia.[1,2] Calcium concentration in serum usually is normal or slightly decreased, and phosphorus in plasma is often low, but on ocassion may be normal or even slightly elevated. Occasionally however, calcium concentrations may fall to extremely low levels leading to hypocalcemic tetany. These variations have been interpreted as indicating differing levels of parathyroid activity. Reifenstein[3] has suggested that normal calcium concentration and low inorganic phosphorus values indicate marked hyperparathyroidism, low calcium and phosphorus indicate a moderate parathyroid response, while low calcium with tetany and high phosphorus means a failure of the parathyroid response. While this view has gained wide acceptance, it has never been proved conclusively, and Nelson[4] has stated that the mechanism of rachitic hypocalcemic tetany remains obscure. Although some workers have shown elevation of calcium concentrations by parathyroid hormone in rachitic subjects,[5] the problem is further complicated by reports that tetany associated with rickets or osteomalacia is sometimes refractory to administered parathyroid hormone,[6,7] thus raising the possibility that low calcium level may result, not from a failure of the parathyroid gland to keep pace with increased demands, but from an acquired failure of bone and kidneys to respond to increased circulating parathyroid hormone. Such a state of tissue refractoriness may constitute a form of secondary "pseudo-hypoparathyroidism." Finally the whole problem must be viewed in the light of current opinions regarding the action of the parathyroids. It has been suggested[8,9] that the two actions of these glands, i.e., calcium mobilizing effect and phosphaturic effect, are independent and may be mediated by separate hormones. Recent work however has suggested that the hormone may consist of a single polypeptide chain which mediates both effects.[17]

These unresolved problems prompted the present study, which attempts to elucidate the role of the parathyroid glands in the pathogenesis of tetany in rickets. An endeavor will be made to relate the calcium level and radiologic findings to the degree of parathyroid activity represented by the phosphorus excretion index (PEI) of Nordin and Fraser,[10] and the plasma inorganic phosphorus levels.

MATERIAL AND METHODS

The findings reported in this study were partly described in Part I[11] and consisted of data obtained from 36 of the Bantu children between 4 and 24 months with active rickets described in that paper. Nine subjects had clinical evidence of tetany as manifested by irritability, carpopedal spasm, or

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ADDRESS: (L.S.T.) 1106 Von Brandis Heights, Petersen Street, Hillbrow, Johannesburg, South Africa.

convulsions, together with a positive Chvostek's sign.

The following investigations were carried out: phosphorus excretion index (PEI) according to our modification of the method of Nordin and Fraser[11]; calcium in serum, according to the method of Langendorf[12]; alkaline phosphatase in serum and inorganic phosphorus in plasma, according to methods described by King and Wootton.[13]

X-ray observations of one wrist, shoulder joint, and the rib ends of each subject, were classified into five grades of severity on the basis of the radiologic findings by a radiologist unaware of the respective biochemical findings. *Grade 1* (±) indicated doubtful irregularity and cupping of the metaphyses of the lower ends of ulna and radius and costochondral junctions. *Grade 2* (+) indicated slight but definite cupping of metaphyses of radius, ulna, and costochondral junctions. *Grade 3* (++) indicated marked irregularity of metaphyses of ulna, radius, and costochondral junctions. *Grade 4* (+++) indicated gross changes of metaphyses of ulna, radius, and costochondral junctions, with well-marked irregularity of upper end of humerus. *Grade 5* (++++) indicated extremely gross rickets with disorganized metaphyses, fractures and chest deformities.

Five patients were in Grade 5 (mean age 14 months), 8 in Grade 4 (mean age 7 months), 11 in Grade 3 (mean age 8 months), 5 in Grade 2 (mean age 7 months), and 2 in Grade 1 (mean age 6 months). Five patients could not be classified because of unsatisfactory x-ray pictures.

RESULTS

All nine patients with tetany had calcium levels less than 3 meq/liter. Two of these subjects had PEI values exceeding +0.35, while 6 had values below +0.2. The PEI values in the tetanic subjects ranged from −0.10 to +0.93, with a mean of +0.20. In the remaining 27 subjects, the PEI ranged from −0.17 to +1.6, with a mean of +0.51.

TABLE I

RELATION OF CALCIUM CONCENTRATION IN SERUM TO THE PHOSPHORUS EXCRETION INDEX

PEI	*Calcium in Serum*		
	<3 meq/l	*3–4 meq/l*	*<4 meq/l*
	Number of Patients		
<+0.32	7	4	7
>+0.32	2	6	10

The difference between the PEI values in tetanic and nontetanic subjects is statistically significant ($p < 0.001$). Plasma-phosphorus levels in the tetanic group ranged from 2.5 to 5.1 mg/100 ml, with a mean of 3.7, as opposed to a mean of 3.18 for nontetanic subjects. The considerable overlap between the tetanic and nontetanic groups at relativtly low PEI values suggests that patients with less-marked hyperparathyroidism constitute a heterogeneous group. Further analysis was therefore undertaken to separate these patients into homogenous pathophysiologic entities.

In order to avoid bias, patients with relative hypoparathyroidism were separated from those with marked hyperparathyroidism simply by dividing the subjects into two equal groups of 18—those with PEI's of less than +0.32 and those with PEI's of more than +0.32. A similar arbitrary division was carried out on the basis of the plasma phosphorus level. A level of 3 mg/100 ml divided the patients into two equal groups of 18 patients.

Table I shows the calcium concentrations in serum in the subjects according to a PEI of less than or greater than +0.32. The uneven distribution is not quite statistically significant on analysis of variants ($p < 0.2 > 0.05$). Table II shows the calcium levels in the subjects according to phosphorus levels greater or less than 3 mg/100 ml. Analysis of variants shows the uneven distribution to be statistically significant ($p < 0.05$).

Figure 1 and Table III illustrate the re-

TABLE II

RELATION OF CALCIUM IN SERUM TO PHOSPHORUS IN PLASMA

Phosphorus	*Calcium in Serum*		
	<3 meq/l	*3–4 meq/l*	*>m meq/l*
	Number of Patients		
>3 mg/100 ml	7	2	9
<3 mg/100 ml	2	8	8

lationship of various biochemical data to radiologic severity of the bone changes. PEI values are highest in Grade 5, lowest in Grade 4, and intermediate in Grades 3 and 2. Grade 1 is not considered, because only two patients were in this group. Analysis of varients shows that these differences are significant ($p < 0.05$). Calcium values in serum are almost identical in Grades 5, 3 and 2 but low in Grade 4. This difference is statistically significant ($p < 0.01$).

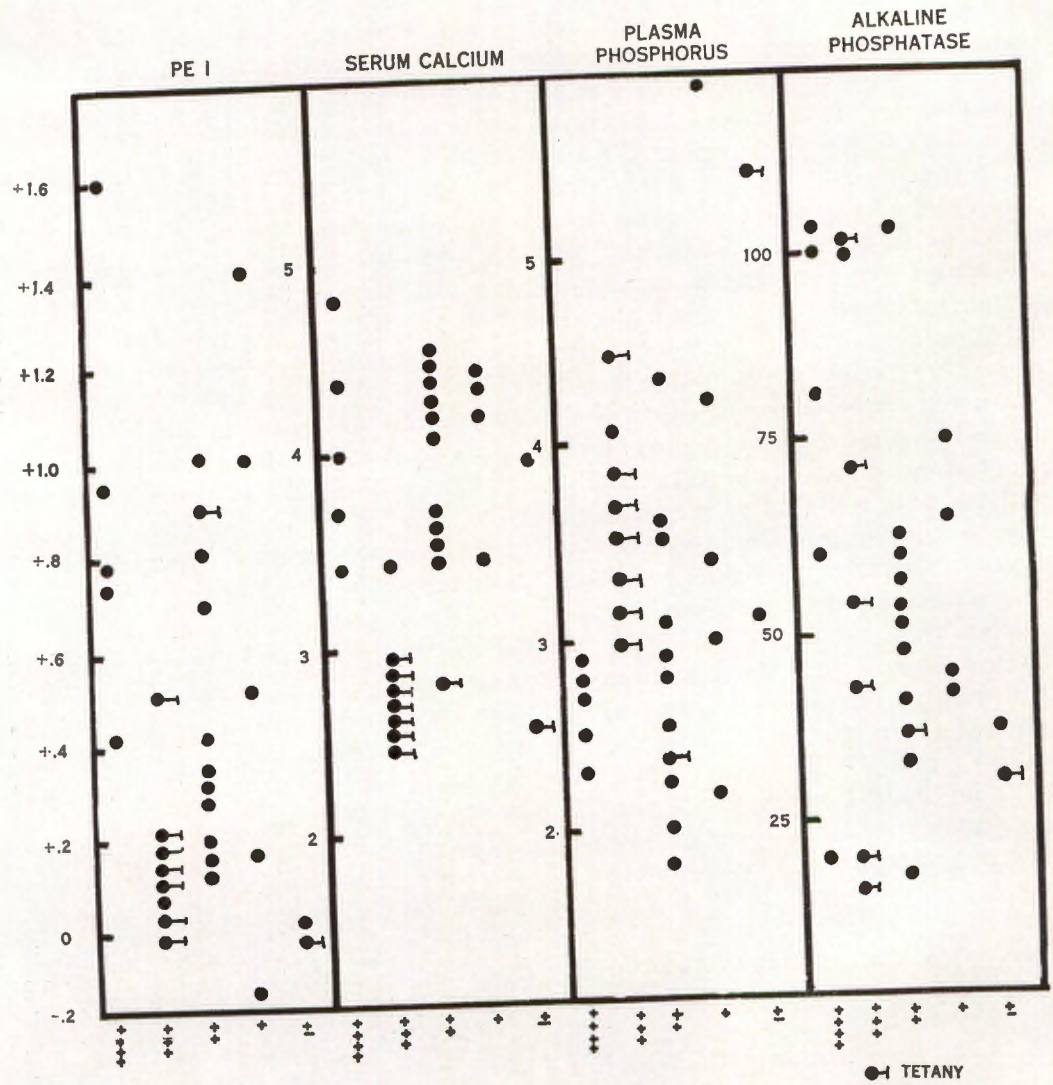

FIG. 1. Relation of phosphorus excretion index, calcium in serum (meq/l), phosphorus in plasma (mg/100 ml), and alkaline phosphatase (King-Armstrong units) to the degree of radiologic severity of infantile rickets.

TABLE III

THE MAIN BIOCHEMICAL FEATURES IN RELATION TO RADIOLOGIC SEVERITY OF RICKETS

Grade	*Cases (no.)*	*Calcium (meq/l)*		*Phosphorus (mg/100 ml)*		*PEI*		*Alkaline Phosphatase (KA units)*	
		Mean	*Range*	*Mean*	*Range*	*Mean*	*Range*	*Mean*	*Range*
5 (++++)	5	4	3.4–4.8	2.5	2.2–2.8	+0.95	+0.5 to +1.6	72	18–108
4 (+++)	8	2.78	2.5–3.4	3.7	3.0–4.5	+0.15	−0.04 to +5	57	16–100
3 (++)	11	3.9	2.7–4.6	2.8	1.7–4.3	+0.46	+0.1 to +9	48	18–106
2 (+)	5	4.1	3.4–4.4	3.9	2.3–6.6	+0.56	−0.17 to +1.4	51	35–70
Normals	8	4.5	4.2–4.8	5.5	4.5–6.3	−0.14	−0.22 to +0.04	20	15–24

Plasma phosphorus levels are low in Grades 5 and 3 and high in Grades 4 and 2. These differences are also significant ($p < 0.05$). The differences between the alkaline phosphatase levels in each of the grades are not significant.

The data of individual patients are given in Table IV. Renal function was assessed in the tetanic and nontetanic groups by the following methods: (*a*) plasma creatinine in all patients, (*b*) blood urea in all patients, and (*c*) glomerular filtration rates (endogenous creatinine clearance) in three nontetanic and two tetanic subjects not included in this series. There was no statistical difference between the two groups (Table V).

Figure 2 shows the relationship between phosphorus in plasma and calcium in serum, with differential plotting of varying degrees of radiologic severity and parathyroid activity. Values for patients with very severe rickets (++++) and high PEI values (> +0.2) do not overlap values for moderately severe cases (+++) with relatively low PEI values (PEI < +0.2).

COMMENT

It has been shown that the PEI is increased in children with Vitamin D deficiency rickets.[11] This index is a function of the capacity of the renal tubule to reabsorb phosphate, and elevation of the PEI is strong presumptive evidence of parathyroid hyperfunction. These findings conform with the hypotheses of earlier workers[14] and agree with the observations of Nordin and Fraser[10] in adults with osteomalacia secondary to the malabsorption syndrome. It has also been demonstrated that children with rickets who had relatively high phosphorus levels had relatively decreased parathyroid activity on the basis of the PEI when compared with children with low phosphorus levels. A direct correlation of moderate significance was found to exist between the PEI and alkaline phosphatase levels.

Certain difficulties arise when the calcium concentration in serum is compared with the PEI or the phosphorus concentration in plasma. These difficulties result from the fact that the rachitic subjects presented do not represent a homogeneous group and may belong to any of several categories. This applies particularly to patients with evidence of relatively low parathyroid activity. Such subjects may have (*1*) very mild but active rickets, (*2*) biochemical but not radiologic features of commencing healing, and (*3*) parathyroid "failure."

It is not surprising, therefore, that no direct correlation can be demonstrated between the PEI and the calcium levels (except for those patients with very low calcium levels and tetany). This overlap of differing populations cannot be separated on the basis of the alkaline phosphatase concentration because of the extremely wide range that was encountered, and man-

TABLE IV

DATE FOR INDIVIDUAL TETANIC AND NONTETANIC PATIENTS

Case Number	Age (mo.)	Nutrition*	Alkaline Phosphatase	Serum Calcium	Plasma Phosphorus	PEI	Plasma Creatinine	X-ray Grade
Tetanic Subjects								
1	4	Good	54.0	2.6	3.8	+0.49	0.7	+++
2	7	Poor	19.2	2.9	3.7	+0.08	0.69	+++
3	12	Good	53.0	2.8	3.5	+0.01	0.67	+++
4	3	Good	100.8	2.5	4.5	+0.12	0.7	+++
5	5	Poor	40.0	2.7	3.0	+0.14	0.88	+++
6	4	Poor	29.0	2.6	5.21	−0.10	0.66	±
7	7	Good	75.0	2.8	4.1	−0.04	0.77	++
8	12	Poor	42.5	2.7	2.5	+0.93	0.7	+++
9	8	Poor	16.0	2.5	3.4	+0.09	0.69	+++
Nontetanic Subjects								
1	9	Poor	..	3.7	2.3	+0.24	0.69	++
2	6	Good	40.5	3.4	2.3	+0.54	0.75	+
3	17	Poor	17.8	3.4	2.2	+0.50	0.66	++++
4	7	Good	38.7	4.3	2.9	+0.29	0.71	++
5	3	Good	53.0	4.5	4.5	+0.39	0.73	++
6	6	Poor	51.5	4.6	2.0	+0.98	0.71	++
7	6	Poor	27.3	3.6	2.8	+0.33	0.65	++
8	18	Poor	46.0	4.2	4.3	+0.28	0.675	++
9	5	Good	108.0	3.5	2.2	+0.81	0.79	++
10	6	Poor	76.0	4.0	2.6	+0.77	0.75	++++
11	10	Poor	68.5	3.4	3.9	+0.23	0.81	..
12	6	Good	52.3	4.5	2.53	+0.14	0.68	++
13	17	Poor	107.0	3.6	2.8	+0.74	0.72	++++
14	6	Good	72.0	4.6	3.0	+1.4	0.69	+
15	8	Good	50.0	4.2	3.05	−0.02	1.05	±
16	9	Poor	36.7	4.3	6.6	−0.17	0.71	+
17	6(±)	Good	46.5	4.4	1.6	+0.68	0.72	..
18	5	Good	53.7	3.3	4.4	−0.072	0.68	..
19	7	Good	34.0	4	2.9	+0.11	0.63	+
20	5	Good	60.0	4.4	3.2	+1.0	0.66	+
21	18	Good	60.5	4.3	2.6	+0.95	0.73	++++
22	6	Poor	..	3.6	2.1	+0.21	0.72	..
23	7	Poor	67.0	4.3	5.5	+0.32	0.75	..
24	10	Poor	100.0	4.8	2.7	+1.6	0.92	++++
25	5	Poor	33.0	3.6	3.6	+0.1	0.72	++
26	10	Poor	17.0	4.2	3.5	+0.2	0.78	++
27	5	Good	100.0	3.4	3.4	+0.08	0.7	+++

* Good nutrition = weight exceeding 3rd percentile.

ifestly the PEI and inorganic phosphate levels in plasma cannot be used for the purpose.

Tables I and II taken in conjunction show that patients with relative hypoparathyroidism (i.e., PEI, $< +0.32$; phosphorus, > 3 mg/100 ml) tend to have a bimodal distribution of calcium concentration in that the calcium levels are either normal (> 4 meq/l) or very low (< 3 meq/l), with few patients having intermediate calcium levels. Clearly such a distribution suggests that two types of subject are being grouped together, i.e., patients with very mild ric-

kets (high calcium levels) or patients with parathyroid "failure." Subjects with early healing rickets might fall into either category, since it has been shown that tetany may be precipitated by the administration of calciferol to patients with rickets, presumably as a result of suppression of the parathyroid glands consequent to increased calcium absorption from the bowel and the rapid incorporation of calcium into the excess uncalcified bone matrix.[4] The bimodal distribution is illustrated by Figure 2, if the graph is rotated so that the serum calcium concentrations come to lie along the horizontal axis.

Tables I and II also illustrate the fact that in only two instances did profound hypocalcemia occur where there was evidence of marked hyperparathyroidism. These two subjects art of considerable interest since severe hypocalcemia developed with PEI values of +0.93 and +0.49 respectively.

Assuming that parathyroid failure is the cause of the hypocalcemia, it must be concluded that failure of the calcium-mobilizing component of parathyroid hormone may occur before or independently of failure of the phosphaturic component. This is a highly speculative hypothesis but attractive because it maintains a unitarian concept of the pathogenesis of rachitic tetany.

An alternative explanation for these findings is that the tetanic children for some reason have impairment of glomerular filtration (GFR) with phosphate retention leading to hyperphosphatemia and a resulting fall in the calcium content. The theoretical and empirical objections to this view seem overwhelming. (*1*) Plasma creatinine and urea levels were identical and within normal limits in both groups. It is unlikely that phosphate retention severe enough to lower the calcium content could occur without some elevation of urea or creatinine. (*2*) The method employed here for expressing phosphate excretion (PEI) refers specifically to tubular function, and it should be unaffected by changes in GFR. Indeed Nordin and Fraser[10] have demonstrated elevation of the PEI in uremic patients with moderate phosphate retention. It would thus be illogical to explain the *depression* of PEI in tetanic subjects on the basis of impaired GFR. (*3*) The clearance of endogenous creatinine was identical in two tetanic and three nontetanic subjects.

It is therefore concluded that the relative decrease of the PEI and elevation of the plasma phosphorus in tetanic patients is tubular in origin, *not* glomerular, and that the most likely explanation is decreased parathyroid activity.

The introduction of a further parameter, the degree of radiologic severity of bone changes, further clarifies the problem of the mixed populations. Three biochemical patterns become evident. Grade 5 (++++) patients with very severe bone changes show the highest PEI values, lowest plasma phosphorus levels, and relatively normal serum calcium concentrations. This suggests a picture of intense parathyroid over-activity. Grades 2 (+) and 3 (++) patients are rather similar and probably do not warrant separate analysis. The PEI values in these

TABLE V

COMPARISON OF MEAN VALUES OF MAIN BIOCHEMICAL FEATURES IN TETANIC AND NONTETANIC SUBJECTS

Subjects	*Serum Calcium (meq/l*	*Plasma Phosphorus (mg/100 ml)*	*PEI*	*Urea (mg/100 ml)*	*Creatinine (mg/100 ml)*	*GFR (ml/min/M²; mean)*
Tetanic	2.7	3.70	+0.20	19.0	0.71	68*
Nontetanic	4.1	3.18	+0.51	17.6	0.71	63†

* Two subjects.
† Three subjects.

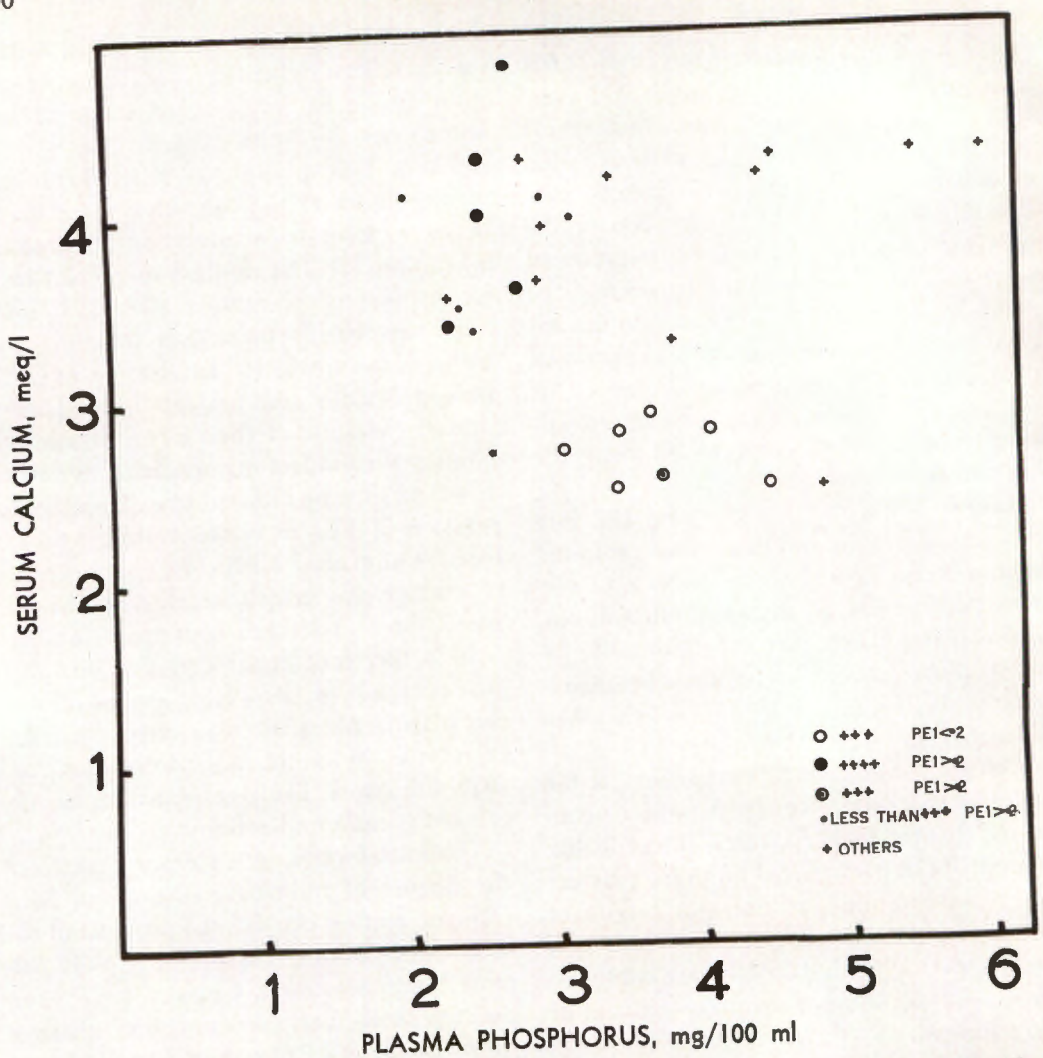

FIG. 2. Relation of calcium in serum (meq/l) to phosphorus in plasma (mg/100 ml) in infantile rickets (key: +++ or ++++ refer to the two most severe radiologic grades).

patients in general are moderately elevated, while the phosphorus concentrations in plasma are low or slightly decreased. Both PEI and phosphorus values show a wide variation. Calcium levels are relatively normal or slightly depressed, with one exception. It is among these patients that mixing of different biochemical variants is most evident and probably accounts for the wide range of both PEI and phosphorus values.

Intermediate between these two groups are the Grade 4 (+++) patients who show significantly lower PEI values and calcium concentrations, and high phosphorus levels. These are the features of relative secondary hypoparathyroidism or secondary pseudohypoparathyroidism.

There are not enough subjects in Grade 1 (+) for detailed analysis.

Several points of interest arise from this analysis. It is clear that very gross rickets and moderately severe rickets are both associated with a well-marked parathyroid response differing only in degree between the two groups. An intermediate group exists, however, in which the parathyroid response is much less intense or even absent. It is in this latter group that most cases of tetany occur. That these subjects form a distinctive group is further borne

one by Figure 2, where it is clear that patients with severe (+++) rickets and relatively low PEI values tend to fall close to each other, with very little overlap, when calcium values are plotted against phosphorus values; whereas patients with severe bone changes (++++) and marked elevation of the PEI lie above and to the left of the former group.

These findings correlate well with previous observations on the incidence of tetany in the malabsorption syndrome,[15] in which it has been found that patients with severe demineralization did not develop hypocalcemic tetany. It seems likely that all subjects with rickets respond initially by developing secondary hyperparathyroidism with moderately severe bone changes and maintenance of normal calcium levels. The subsequent course of the disease depends on whether the parathyroid response is maintained or not.

Should parathyroid activity be maintained or even increased, gross bone demineralization occurs with maintenance of normal calcium levels, as in Grade 5. Should the parathyroid response fail, the degree of bone demineralization is less marked, but a definite tendency to hypocalcemia and tetany develops, as in Grade 4. Sometimes tetany may intervene early, before marked bone changes have occurred or even before overt radiologic signs of rickets appear, due to a premature failure of the parathyroid response to decreased calcium absorption. This is illustrated by one subject in Grade 1 who developed hypocalcemic tetany. This child had no overt radiologic evidence of rickets, but the calcium level was elevated by the administration of small therapeutic doses of vitamin D (5,000 U daily). Early parathyroid failure during the course of vitamin D deprivation might explain some cases of idiopathic infantile hypocalcemic tetany.

The clear-cut distinction between subjects in Grades 4 and 5 is probably the result of fortuitous hospital selection and is not a true reflection of the incidence in the population at large. On the basis of the hypothesis presented herein, it would be expected that Grade 4 patients with high PEI values and normal calcium concentrations should occur. It is likely that these patients do not come to the hospital unless tetany supervenes or the bone disease progresses to the stage of bone deformities, when they would then be classified as Grade 5. It is important in this regard to recall that in a sunny country such as South Africa, active rickets rarely progresses beyond the toddler stage.[16]

The wide range of alkaline phosphatase in each of the grades is difficult to explain. Except for the moderate correlation previously reported with the PEI,[11] no clear-cut correlation could be demonstrated with any of the biochemical or clinical features.

The data presented in this paper leave two important questions unanswered. In the first instance it is not clear whether hypocalcemia results from a failure of the parathyroid gland or from secondary "pseudohypoparathyroidism." Secondly we have not been able to elucidate what factor is responsible for this failure. There appears to be no relationship to the age of the patients or their state of nutrition. These problems are at present under investigation.

ADDENDUM

MN, a 2-month-old Bantu infant, was admitted to the ward for treatment of gastroenteritis and hypertonic dehydration. Following good response to intravenous therapy, the infant was noted to be irritable, with carpopedal spasm; an initial diagnosis of postacidotic tetany was made. The chemical constituents of blood at this stage were as follows: sodium in serum, 135 meq/l; potassium in serum, 4.6 meq/l; chlorides, 104 meq/l; total carbondioxide content, 23.6 meq/l; calcium in serum, 2.7 meq/l; phosphorus in plasma, 3.5 meq/l; alkaline phosphatase, 54 King-Armstrong units; and blood urea, 22 mg/100 ml. Intravenous therapy was stopped, and calcium chloride in a dosage of 5 ml of a 1% solution was given orally every 8 hours. Radiologic examination showed the presence of moderately severe rickets.

During the following week the child remained in continuous tetany with calcium levels on alternate days of 2.5, 2.7, and 2.6 meq/l respectively. During this period the phosphorus in plasma showed progressive elevation, with values of 3.5, 4.2, and 5.2 mg/100 ml. At this stage the patient was given parathyroid extract, 100 units every 6 hours, with resulting elevation of the calcium and depression

of the phosphorus concentration to 4.4 meq/l and 2 mg/100 ml respectively within 36 hours. Administration of parathyroid hormone was stopped, and 24 hours later the calcium concentration had fallen to 2.9 meq/l, with return of tetany, while the phosphorus increased to 3.8 mg/100 ml. Resumption of parathyroid therapy brought about a second prompt increase in calcium concentration (4.4 meq/l) and decrease in phosphorus (2.8 mg/100 ml).

These findings indicate that this patient was highly responsive to parathyroid hormone, both regarding the calcium mobilizing and renal action of hormone; they support the view in this paper that hypocalcemic tetany in rickets results from relative insufficiency of endogenous parthyroid secretion.

SUMMARY

Hypocalcemic tetany does not occur in South African Bantu infants with very gross bone changes of rickets. Rachitic children with hypocalcemic tetany have significantly lower phosphorus excretion indices than those with normal or moderately decreased calcium levels. Tetany appears to occur in a specific group of subjects with moderately severe bone changes, decreased phosphorus clearance, and relatively high plasma phosphorus levels. It is suggested that this group represents either failure of the compensatory parathyroid response or secondary "pseudo-hypoparathyroidism." Certain cases of idiopathic infantile tetany may be the result of premature failure of the compensatory parathyroid response to deficiency of vitamin D.

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RICKETS IN THE TROPICS

SIR,—We were much interested in the investigation of Drs. STRANSKY and DIZON, on rickets in Manila in the Philippines, which was recently published in your Journal (March 1956, page 232). As the above workers point out, present knowledge regarding the occurrence of the disease in the tropics and semitropics is somewhat contradictory. Thus, GELFAND in Southern Rhodesia, and TROWELL in Uganda, have testified to the rarity of the disease among African infants in these territories. At the same time, JELLIFFE at Ibadan in Nigeria, WILSON and WIDDOWSON in India, FELDMAN in Johannesburg, South Africa, and others have drawn attention to the commonness of the disease in crowded urban areas.

At this centre, we have been studying several aspects of the calcium metabolism of the South African Bantu, and hence we became interested in the possible rôle of calcium deficiency in the aetiology of rickets. From a careful examination of available knowledge we have reached the conclusion that it has not been established that a low calcium intake *per se* promotes, still less causes, rickets.[1] Furthermore, we have obtained evidence which reveals that the popular view that rachitic bone is characterized by considerable demineralization is not correct ; only in very severe rickets does the percentage mineral composition of bone (5th rib) become markedly reduced.[2]

However, the primary purpose of this letter is to indicate that the paradoxical situation referred to above has been the subject of a good deal of local enquiry, and over a long period we have been investigating the incidence of clinical rickets in Bantu infants in urban, peri-urban, and rural regions. The investigation, which includes observations on several hundred infants, is now almost complete. In brief, it has become apparent that in crowded urban centres, such as Johannesburg, up to the age of two years and very rarely thereafter, rickets is common and occasionally occurs very severely. In contrast, in the strictly rural areas, rickets has been found to occur far less frequently, and is then usually mild in character. While the basic diet consumed is much the same in all the regions we have studied (at least in so far as the virtual absence of *ingested* vitamin D is concerned) we have been struck by the great difference in the amount of clothing worn. Whereas the urban Bantu baby is usually very well clothed (often more so than the European baby), the rural baby crawls and walks around partially naked. On this account and for other reasons, we consider that degree of exposure to available radiation is the predominating influencing factor.

Our view may seem reasonable enough for the tropics and semitropics ; however, we may point out that much the same conclusion has been arrived at in studies undertaken in regions far to the north. Forty years ago, FINDLAY and FERGUSON carried out their classical investigation on the incidence of rickets in Glasgow, situated in latitude 58° N.[3] A salient finding was that although the diet consumed by the non-rachitic children was only slightly superior to that of the rachitic subjects, of the latter, 40 per cent. were not taken out regularly, while only 4 per cent. of the non-rachitic children had been confined indoors regularly. More recently, RUSTUNG, in an inland Norwegian valley, latitude 65°N., carried out a study on the occurrence of rickets.[4] The incidence of the disease

was found to be high particularly up to school age (30-40 per cent.). The diet was composed mainly of cereals and vegetables, with a variable though usually small supply of milk. RUSTUNG found that freedom from rickets was closely associated with the length of time the children spent in the open air.

We do not, of course, maintain that vitamin D status is the only factor worth considering : we certainly believe that there are other factors, the rôle and importance of which we have been endeavouring to determine. It is our hope that our observations, when published, may contribute to clarify and harmonize the present unsatisfactory state of knowledge.

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Human Biochemistry Research Unit. A. R. P. WALKER.
South African Council for Scientific and Industrial Research,
South African Institute for Medical Research, Johannesburg.

Department of Paediatrics, H. C. FALCKE.
Coronation Non-European Hospital, A. NESTADT.
Johannesburg. HARVEY COHEN.

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CERTAIN BIOCHEMICAL FINDINGS IN MAN IN RELATION TO DIET*

By A. R. F. Walker

Human Biochemistry Research Unit, South African Council for Scientific and Industrial Research, and South African Institute for Medical Research, Johannesburg, Union of South Africa

This paper deals primarily with observations made on the South African Bantu, upon whom, with a number of associate workers, I have been carrying out various investigations over the last ten years. The local Bantu differ from the white population in numerous ways: in diet, biochemistry, hematology, physiology, and pathology. In some respects, these people are the objects of our sympathy; in others, they are most certainly the objects of our envy. In some countries there would seem to be a limited choice of problems in human nutrition to investigate, but in South Africa it is a question, rather, of which fascinating problem one should attack first. In the course of my work I have touched upon many fields, any one of which could well engage the attention of several workers for many years. I have endeavored to investigate some problems intensively; I have merely scratched the surface of others. Although the Union of South Africa is about one sixth of the area of the United States, its white population is about one fourth of that of New York, N. Y.; its total population is less than one tenth of that of the United States. Having a Bantu population living on one's doorstep, so to speak, causes one to realize that in South Africa the fields of research are ripe for harvest and that the laborers are far too few.

Diet

The Bantu of South Africa number about 9½ million; accordingly, they greatly outnumber the white population of about 3 million. In addition, there are about 1 million Eurafricans and one half million Asiatics. Of the Bantu, roughly one third dwell in Native Reserve areas, about one third work on farms owned by white people, and the remainder are urbanized, working in government and municipal departments, in industry, and as domestic servants. These people, therefore, may be observed in various stages of dietary transition, from the primitive living off the land to the urban house-boy consuming a largely Europeanized diet. The Bantu diet, speaking generally, includes a large amount of cereals, which supply 50 to 90 per cent of the total calories in the food consumed. Such cereals, usually whole-ground or lightly milled, comprise maize (corn), "kaffir corn" (*Sorghum vulgare*), and wheat. The maize and kaffir corn products are eaten, not only as a variety of porridges, but as fermented foods (such as *marewu*, *lambalaza*, and kaffir beer). These foods, being traditional, are widely consumed, often in large volume. This particular characteristic will be referred to again. The wheat,

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of course, is consumed as bread (about one half white and one half whole grain bread); its consumption is becoming increasingly popular near and in the large centers of population, perhaps principally because it is a food immediately ready for consumption. A further occasionally important item of diet consists of different types of legumes. Of vegetables consumed, the more common ones, particularly in rural areas, are the pumpkin, sweet potatoes (*Ipomoea batatas*), and various greens. The amount of eggs, meat, fish, and dairy produce eaten, also sugar, is usually much less than among the white population. Briefly and very generally, the diet of these people, according to accepted standards, although usually adequate in calories and gross protein, is low in animal protein and fat, high in carbohydrate and crude fiber, high in certain mineral salts and vitamins, for example, phosphorus, iron, vitamin A, and thiamine, but low in others, for instance calcium, riboflavin, and vitamin D.

This pattern of diet is common; in fact, qualitatively it is the pattern consumed by the greater part of the earth's population. The same pattern of diet was common among our forefathers a century or so ago; moreover, the adoption of such a regimen frequently is forced upon many countries for limited periods by wartime restrictions.

What are the likely effects of the lifelong consumption of such a diet? What are likely to be the biochemical and pathological stigmata of a deficiency, or perhaps of an excess, of nutrients? Those who have participated in discussions on the examination and revision of recommended allowances will know of the heart searching that arises when we ask ourselves: How much do we really know about human needs of nutrients? Often one reads phrases such as "minimum physiological requirements," "marginal and optimal intakes," and "safety margins"; surely such expressions bear witness to the incompleteness of our present knowledge of the subject. Moreover, those of us who are white and live alongside a nonwhite population such as the South African Bantu must confess to the exasperation we often experience on considering whether these people are or are not short of this or that nutrient, particularly when, as often occurs, the relevant deficiency stigmata are not apparent.

I now cite a few examples of nutritional situations and their ramifications confronting those of us in South Africa who are interested in the broad picture of the diet, in biochemistry, and in the clinical state and pathology of the Bantu. The examples to be described, which bear on protein, fat, calcium, iron, niacin, and vitamin C, in some instances call for a revision of current thought on diet and certain diseases; in others, they indicate a need for the reassessment of recommended allowances of nutrients; while other examples touch on phenomena deemed to be abnormal or even pathological, but which nevertheless would seem to be the normal response of healthy persons to the pattern of diet consumed.

Protein

The first point to be emphasized is that, in contrast to many other African populations, the diet of the South African Bantu older child and adult is characterized neither by deficiency of gross protein nor of specific amino acids.

According to recent local dietary surveys,[1-3] the gross protein intake of the adult South African Bantu is approximately adequate on the 1 gm./kg. basis. Indeed, since the bulk of the energy value of the Bantu diet is derived from cereals (roughly 400 to 600 gm. per diem, depending on the region), and since significant underweight (perhaps 10 to 15 per cent less than weight/height tables indicate) is not a feature of these people, the gross protein intake, in the main, *cannot* be seriously low. This observation must not be taken to imply that *all* local Bantu adults obtain adequate protein. Obviously, among these people, as among any other population group, a proportion ingest insufficient of the nutrient. The fact remains that a low total protein intake is not *characteristic.*

Concerning the intake of amino acids, if one takes the amino acid needs of young American adults reported by Rose[4] and assumes that the figures are applicable to the Bantu pattern of diet, then simple calculation shows that these amounts are contained in about 300 to 350 gm. maize or combination of cereals—an amount contained in the diet of most Bantu. Indeed, when one considers the *total* diet of these people, the diet usually contains more than the remommended allowances of amino acids suggested by Rose, that is, the amounts that were multiplied by two to provide a "safety margin." Patwardhan,[5] from an examination of diets consumed in several different countries, has also concluded that where the calorie needs of a population are met and satisfied largely from cereals, the intakes of the different amino acids are reasonably satisfactory. However, as Patwardhan pointed out, one does not know whether amino acid needs are or are not significantly affected by different patterns of diet. The foregoing does not apply to the child, whose diet, from weaning until he reaches school age, is very likely, especially at the beginning, to be deficient in protein, among other things. Nevertheless, taking into account, first, the level of intake of gross protein of the local Bantu and, second, the increasing evidence strongly suggesting that the protein requirements of man are less than has been thought previously,[6-8] one's impression is that the diet of the local adult Bantu is deficient neither in gross protein nor, presumably, amino acids.

I now propose to comment on lactation, because it is believed by many to be promoted by or even dependent on a greatly increased protein intake, and on liver disease and gynecomastia, both of which are regarded by many as expressions of chronic protein malnutrition.

Lactation

To promote satisfactory lactation, dietary standard bodies recommend increased daily allowances of a number of nutrients, including, *inter alia*, 25 gm. protein, of which one half should be of animal origin. The actual diet suggested for nursing mothers is well known—so much milk, meat, eggs, fruit, vegetables, and other such foods. The point to be emphasized here is that Bantu mothers do not get such a diet, yet they lactate very well, producing milk of satisfactory quantity and quality, and often for prolonged periods. Locally,[9] it is believed that there is parity in clinical state and rate

of growth between exclusively breast-fed Bantu and white infants up to six months; indeed, Welbourn,[10] also Kark (personal communication), maintain that for this period Bantu babies (among whom self-demand feeding is the rule) grow perhaps more rapidly than do white babies. Quantitatively (at least for the first six months) and qualitatively, therefore, Bantu breast milk must be regarded as satisfactory. Chemically, mean values for the main constituents in Bantu breast milk compare very favorably with those of white mothers' milk.[11, 12] Incidentally, Bantu breast milk has a higher mean protein concentration, namely, 1.35 gm. per cent, than the figure of 1.06 gm. per cent given by Macy[13] for mothers' milk in the United States and 1.19 gm. per cent given by Kon and Mawson[14] for the milk of mothers in Great Britain. Concerning the amino acid composition of the protein, determinations have been made only with regard to methionine and tryptophan; the mean concentrations of both have been found by us to be close to those reported for the milk of white mothers.[15]

It is only fair to point out that among African populations elsewhere, whose diet is lacking in several respects, lactation proceeds less satisfactorily.[16] Nevertheless, it should be emphasized that there are many instances where a measure of breast feeding, occasionally to a surprising degree, has been carried out despite consumption of a poor diet; as, for example, during World War II, at Leningrad during the siege, in starving Holland in 1944, in the Japanese Prisoner of War camps, and even at Belsen Concentration Camp in Germany.[11, 12]

In view of this excellent performance by the Bantu mother, how is she herself affected? First, in regard to the magnitude of the drain sustained by her: during a six-months period she yields about 16 kg. (35 lb.) of total solids. Her own body contains about 18 kg. (40 lb.) total solids. On this particular basis, therefore, during the period mentioned, she gives almost the equivalent of herself in gross nutrients. If she does not eat enough to compensate for this drain, she must lose weight, unless the percentage composition of her body alters. However, she does not seem to lose weight; indeed, our own information suggests that the weight-for-height ratio of such women is possibly greater than that of white lactating women; in veterinary parlance, the successful lactation described is not, therefore, a case of "milking the flesh off the cow's back." Therefore, there can be no doubt that, broadly speaking, the lactating Bantu mother obtains her gross needs of nutrients.

But what of disease—eclampsia, for example? Evidence indicates that Bantu women suffer less than white from this condition. Hipsley[17] considers that a broad correlation obtains between crude fiber intake and eclampsia—the greater the fiber intake, the less the incidence of eclampsia. The Bantu diet is certainly high in crude fiber.

Other comparisons have been made. In Johannesburg, in 1941, Heyns,[18] assisted by Shippel, compared 5059 white women with 1433 Bantu women. These investigators reported that the behavior of the Bantu mothers was superior in all respects. Of the Bantu mothers, 0.56 per cent required operative delivery, as against 5.24 per cent among the white mothers. The maternal mortality of the former was lower. The incidence of stillbirth in the Bantu

was 3.5 per cent, a figure less than the corresponding figure of 4.2 per cent for Scotland[19] for the same year. The performance of the Bantu mothers is enhanced in view of the finding recorded by Heyns and Shippel that the Bantu baby, despite a slightly lower weight at birth has a head as big as that of a white baby, yet the pelvic aperture in the Bantu averages about 10 per cent less in area than that of white mothers.

To return to the subject of diet and lactation: one cannot help wondering whether the "vulnerability" of pregnant and lactating women, particularly the former, is perhaps being overstressed. A century ago, among Western populations, large families were usual. I think that it was the demographer Alfred J. Lotka who stated that in the United States, less than a century ago, families including about eight children were almost the rule. In Britain, Sir Walter Scott was a ninth child, Samuel Taylor Coleridge a tenth, John Wesley a fifteenth, and Charles Wesley an eighteenth. Were the nutritional disabilities attached to repeated childbearing and lactation so manifest, relevant information would surely have appeared in contemporary literature or been handed down to us. Admittedly there is much more that one would like to know about the nutrition, biochemistry, physiology, and other aspects of the long-lactating Bantu woman. On the other hand, in spite of this lack of knowledge, two inferences would seem unchallengeable: (1) provided there is a sufficiency of primarily cereal calories, excellent lactation is feasible for prolonged periods; and (2) the failure of the huge proportion of white mothers to lactate satisfactorily can scarcely be ascribed to an inadequate diet. In other words, the role of dietary, as against nondietary factors in human lactation, is overemphasized.

Liver Dysfunction and Disease

In the tropics and semitropics, liver dysfunction and disease are very common among the indigenous populations, and such conditions often are attributed, directly or indirectly, to a low protein intake, or to single or multiple deficiencies of amino acids.[20, 21] One looks askance at this widely accepted etiology because liver disease is common among the Bantu, yet, as stated previously, their diet is characterized neither by a low protein intake nor specific amino acid deficiencies.

Liver dysfunction, insofar as it is reflected by the distribution of the plasma protein fractions and the various precipitation tests on serum, is common in the South African Bantu, being present in more than two thirds of adults examined. Apparently the condition is not improved by the consumption of an adequate diet for protracted periods.[22] Such dysfunction is not accompanied by specific pathology. Concerning liver disease, in a paper by Higginson, Grobbelaar, and myself[23] three types of lesions are described: (1) the fatty liver of kwashiorkor, rarely followed by fibrosis and necrosis; (2) a fine symptomless portal fibrosis, most frequently seen in the second half of life and usually associated with heavy hemosiderin deposition; and (3) a severe cirrhosis, most frequently of postnecrotic origin and showing no specific age trend. More than half of the livers in this third group develop primary malignant change. Briefly, the view is taken that in infancy liver damage is

widespread and that, although this damage is not usually recognizable histologically, it is demonstrable by biochemical tests and is undoubtedly caused primarily by malnutrition. Such damage is believed to predispose the liver to the action of factors that precipitate liver disease in adult life. For the local Bantu, it seems probable that such factors include abnormal iron deposition (siderosis), hepatotoxic viruses and, possibly, toxic drugs. There appears to be no adequate evidence that the nutritional factors that so readily induce hepatic damage in small animals (diets, *inter alia*, low in protein) are responsible for the liver lesions noted in Bantu older children and adults

Gynecomastia

This abnormality, enlargement of the male breast, like liver disease, is believed or suspected by many to be an expression, directly or indirectly, of chronic protein malnutrition.[21, 24, 25] Certainly, gynecomastia is common among the Bantu of Southern Africa but, for the reason previously cited, one is not happy over the suggested etiology.

In Johannesburg, at Baragwanath Non-European Hospital (1500 beds), Higginson and Simpson are investigating the incidence of the condition in a series of consecutive post-mortems. Thus far, among 200 adults, they have found a discrete mass exceeding 2 cm. depth in 2 per cent of subjects. At the Witwatersrand Native Labour Association Hospital, also in Johannesburg, about 1000 young Bantu workers (18 to 40 years) from various regions in Central and Southern Africa pass through weekly for medical examination prior to service on the Gold Mines. The incidence of slight or moderate gynecomastia among them is not known, but observations indicate that an average of about one subject per week (0.1 per cent) is known to suffer from *very marked* gynecomastia, that is, having breasts of about 10 to 15 cm. diameter. Such breasts are indistinguishable in appearance and texture from those of young nulliparous women. Since gynecomastia of this type and severity does not appear to have been previously reported, our findings will be described in some detail.

Twenty-one subjects have now been studied by my colleagues and myself. All subjects appeared in good nutritional condition: no evidence of previous dietary privation could be elicited. There was no bias regarding region of origin; that is, gynecomastia did not appear to occur preferentially in subjects from countries in Central Africa, where the nutritional situation is less favorable than in South Africa. Evidence indicated that the gynecomastia developed usually at the time of or within a few years after puberty. Some subjects had been affected for as long as ten years. The enlargement was usually bilateral, nontender, and there was no exudate. These features are in contrast to those observed in the gynecomastia reported to occur occasionally during recovery from malnutrition and undernutrition, for example, among United States servicemen rehabilitated from Japanese P. O. W. camps. Among such affected persons, Klatskin and his co-workers[26] found the mass to be small (1 to 2 cm. diameter) and tender, and sometimes it was possible to express fluid. Two features have been noted about a proportion of the Bantu subjects thus far examined which, provided one is able to establish them satis-

factorily, would seem of considerable importance. First, about a third of the subjects maintained that the condition was present in their fathers and occasionally in their brothers, thus introducing a possible familial factor into the etiology. Second, almost all subjects asserted that they were not apathetic regarding their sexual desires, and about a third maintained that they were fathers of children. According to current concepts in endocrinology, such behavior would not be expected. Those who have carried out investigational work among nonwhite people will appreciate the difficulties attached to validating these two findings, particularly the second.

Regarding other features, the hair in axillae and pubes appeared masculine in distribution. Apart from the enlarged breasts, the body configuration was likewise masculine in character. In three quarters of the cases, the span exceeded the height by 4 to 8 cm. In all cases except one the genitals appeared normal. The exception had undescended testes. In all subjects, including the last, the voice had broken. About a third had slight enlargement of the liver; but this feature is not believed to have etiological significance, bearing in mind the equal incidence of hepatomegaly in Africans without gynecomastia. According to the study of Higginson and Simpson already referred to, no correlation is apparent between the presence of gynecomastia and of liver disease (fibrosis, cirrhosis, carcinoma). Furthermore, it may be of interest to add that Higginson and Oettle[27] have found carcinoma of the male breast to be less common among Bantu males than among white males.

Turning now to the biochemical side: briefly, data on serum protein fractions and the various precipitation tests reveal no greater abnormality in subjects affected with gynecomastia than in subjects without the disease. Incidentally, no evidence of liver impairment was found by Klatskin and his co-workers[26] on United States prisoners of war with gynecomastia. A small number of tests for ketosteroids, hydroxysteroids, and ketogenic steroids have shown values lying within normal limits. A limited number of determinations of total urinary estrogens and of component fractions, estradiol, estriol, and estrone, have been made locally by Bloomberg, Higginson, and Keeley (private communication). Thus far, the endocrine picture emerging is nonspecific, that is, the picture in gynecomastia subjects does not differ substantially from that in nongynecomastia subjects. Biochemically, therefore, nothing specific has come to light at least insofar as present studies have revealed.

Regarding the etiology, it will be clear already that the type of gynecomastia seen in the Bantu of Southern Africa, as an entity differs in several respects from the gynecomastia sometimes noted during rehabilitation from malnutrition and undernutrition. The common view that gynecomastia in the African is an expression of habitual protein malnutrition cannot be accepted as established, at least insofar as the local Bantu are concerned. Likewise the view that hepatic disease in these people impairs the normal inactivation of hormones produced by the adrenals and gonads still remains a suggestion. This scepticism does not imply, of course, that the liver is not involved: it merely questions the *modus operandi* suggested. One prefers to consider that injury to the liver and, possibly, to other organs sustained by African infants at weaning time and thereafter may provide a substrate suitable for the

development of gynecomastia in later life, such development not being prevented by adequacy of habitual protein intake. The nature of the precipitating factors is not known, although B. J. P. Becker, here at the Institute, has suggested that the estrogenic and other properties of the numerous herbal and other pharmacological preparations used by these people merit serious investigation.

It must be re-emphasized that, in making these and previous comments, adults and perhaps older children are in mind, and *not* the very young. Indeed, it will be appreciated that if only there were a more satisfactory food intake at weaning time and immediately thereafter, there might well be a lower incidence of liver disease and of other diseases later in life. However, the mere provision of milk or milk-substitute foods at weaning time will be insufficient; what will also be required is education in preparing these foods for consumption. In Johannesburg we have found that even when nourishing infant foods are purchased, they are almost invariably made up in far too dilute a form by Bantu mothers.[28]

Fat

The fat intake of the South African Bantu is low; a rough average of about 40 gm. per diem is consumed, providing about 15 per cent of the total calories.[1-3] More than half of the fat is "hidden," being contained in the lightly milled maize products, also in legumes. I refer to three aspects of the fat metabolism picture of these people: (1) the low serum cholesterol levels and the low incidence of severe atherosclerosis; (2) the elevated serum cholesterol levels that are a feature of obese Bantu women; and (3) the high excretion of fecal fat on the "high residue" diet of these people.

Low fat intake, serum cholesterol concentration, and atherosclerosis. No significant difference has been found in mean cholesterol levels of newborn Bantu and white infants.[29] In later life, however, serum cholesterol levels of the Bantu are lower, and the age trend of increase slight in comparison to corresponding data on white subjects.[30] Collaborative current studies show that beta lipoprotein cholesterol concentrations are low, as are also the ultracentrifuge flotation values. Investigation has revealed that severe atherosclerosis in the aorta and in coronary vessels is rare, and that the death rate from coronary heart disease among adult Bantu hospital populations in Johannesburg is about a tenth of that in corresponding United States and Danish hospital populations.[31] A comprehensive study of the chemical composition of total aorta from Bantu and white subjects, in age groups from 20 to 80+ years, has confirmed the far lesser degree of quantitative atheromatous change in the Bantu.[32] The difference in death rates from coronary heart disease in the two racial groups is much greater than the difference in extent of atheroma. In other words, some Bantu do get moderately severe atherosclerosis, yet such lesions, for reasons not yet clear, very seldom lead to occlusion. Incidentally, evidence suggests that among the local Bantu there is no sex bias either of vascular lesions or of death rates from coronary heart disease.[33]

It has been pointed out elsewhere[34, 35] that the low fat intake of the Bantu

is but one characteristic of their diet, just as a low incidence of the more serious complications of severe atherosclerosis is but one feature of their disease pattern. It would therefore seem unwise to draw categorical conclusions as to the extent of the relationship involved: it is better at present simply to recognize that the Bantu, living on a diet that is, *inter alia*, low in fat, very seldom die from coronary disease.

However, I now mention a nondietary factor (this, I am afraid, is not a biochemical matter) of possible etiological importance. In a recent paper Mann, Nichol, and Stare,[36] in commenting on the low values found for beta lipoprotein and cholesterol levels in the sera of Nigerians, suggest that a large muscle mass or a large muscle expenditure may well be the effective agent, and that this, and not the diet, is the important element in preventing hyperlipemia and perhaps atherosclerosis. In the South African Bantu, the existence of a large muscle mass—large, that is, as compared with that in the white population—would seem questionable both from anthropometrical and from post-mortem observations. A large muscle expenditure among these people, with the possible exception of Bantu mine workers and a few other groups, is hardly in accord with everyday observations. Obviously, this statement does not mean that these people are lazy, but rather that excessive activity is not characteristic of the Bantu, who, in the past, were primarily a pastoral population. However, there is one feature that might be relevant to the conception of Mann and his colleagues, and that concerns the inexplicably high degree of motor fitness. Thus, using the Harvard step test on groups of somewhat poorly nourished Bantu school children, le Riche *et al.*[37] found that 50 per cent were in excellent or superior physical condition, in contrast to about 5 per cent of 600 children in a private school in the United States similarly rated, as quoted by le Riche *et al.* Similar observations, including other additional tests, have been reported by Morrison *et al.*[38] on Bantu mine workers. More recently, Kloppers and his co-workers, in an unpublished study, compared adult Bantu with corresponding white long-term prisoners on step test performance and found the Bantu to be virtually inexhaustible. A further study of great interest in this regard is that of Gopalan and Ramanathan.[38a] These workers compared fat intake, serum cholesterol levels, exercise, and incidence of coronary heart disease among groups of Indian adults, namely, officers and other ranks of the Indian Defence Force. The fat intake, about 90 to 120 mg. per diem, of the officers was composed of hydrogenated vegetable fat and animal fat (2:1); of the other ranks, chiefly sesame oil (40 per cent linoleic acid). In the former group, cholesterol levels rose from 154 mg. per cent (20 to 29 years) to 201 mg. per cent (40 to 49 years); in the other ranks there was no rise, the mean value being about 145 mg. per cent. The latter group, in contrast to the former, was accustomed to habitual strenuous physical exertion. The incidence of coronary artery disease among the officer class was 23 times that among the other ranks. It might be added that the level of physical fitness of United States recruits in World War II was very disappointing.[39] There can be little doubt that activity and physical fitness are implicated in the etiology of the disease under discussion, although to what extent the feature described has a

bearing on the relative freedom of the Bantu and other similar populations from atherosclerosis awaits investigation.

Elevated serum cholesterol concentrations in obese Bantu women. As already stated, the diet of the Bantu seldom is deficient in energy value, cases of severe undernutrition being very rarely encountered. In this section, the point of interest that I wish to emphasize is that, whereas obesity is almost nonexistent in Bantu males, it is very common in Bantu young women, who, moreover, have significantly elevated serum cholesterol values; the causes of both are unknown. Thus, among 50 nonpregnant, nonlactating Bantu women, 20 to 30 years old, all 20 per cent or more overweight when judged by Western tables, the mean serum cholesterol value was 224 mg. per cent. This value is much higher than the figure of 175 mg. per cent found for a like number of nonpregnant, nonlactating, nonobese Bantu women of the same age group. The foregoing would seem to be an accentuated example of the tendency to obesity and slightly raised serum cholesterol values noted by Keys *et al.*[40] among the women of the poorer groups investigated in Madrid, Spain. In the case of the Bantu obese women, according to unpublished observations by Higginson, post-mortem examination of the blood vessels does not reveal atheromatous lesions any greater in frequency or extent than those present in nonobese Bantu women. Here, then, is a problem of interest, a portion of Bantu women who develop obesity and significantly elevated serum cholesterol levels; the latter feature, however, is not indicative of increased atherosclerosis.

High excretions of fecal fat on a "high residue" diet. According to observations on Bantu and white subjects I made some time ago, on a diet containing a modicum of white bread the amount of dry feces accruing per diem is about 20 to 25 gm. When brown bread is substituted for white, the figure rises to about 30 to 35 gm. When the amount of brown bread eaten is increased to about 1 lb. per diem, the yield of dry feces increases to about 40 to 50 gm. With a higher consumption of coarse cereal products, such as quite commonly occurs with Bantu, at least in rural areas, the figure occasionally exceeds 100 gm. dry feces per diem. Enormous stools of this type were also noted by McCance and Widdowson[41] in their *Experimental Study of Rationing*, when their brown bread consumption was about 3 lb. per diem, and were also reported in later studies by these workers when using other high cereal diets.[42, 43] Accompanying this huge increase in stool weight, the time of passage of material through the digestive tract may be reduced to a third of that obtaining on a white bread dietary. Taken together, the changes described, seemingly inherent in altering a diet from one of a "low" to one of very "high residue," may entail as much as a fifteenfold increase in rapidity per unit volume of fecal material traversing the bowel. The relevant changes in intestinal microflora, in biochemistry and metabolism, and various other ramifications appear to have evoked very little interest in this particular field of nutritional science. The special feature to which I draw attention is the excessively high excretion of fecal fat voided under these circumstances. In certain studies of McCance and his co-workers[42, 43] involving the feeding of very high cereal diets to humans, the amounts of fat voided reached 22 gm. per diem, giving an apparent ab-

sorption of 54 per cent on the high wheat diet, and 68 per cent on the high oats diet. In two Bantu prisoners whom I observed for 21 days and who were ingesting about 26 gm. fat, the fecal fat voided was found to average about 13 gm. per diem, giving an apparent absorption figure of 50 per cent.[44] In the everyday diet of white populations, a percentage fat absorption figure less than 90 per cent usually is regarded as pathological. Yet the phenomenon described cannot be regarded as of pathological significance, for the extraordinary high excretions of fecal fat are surely the normal response evoked in normal people by the consumption of a diet very high in whole grain or lightly milled cereal products. McCance *et al.*[41-43] incline to the view that much of such fecal fat is composed of undigested fat. Elsewhere,[45] I have suggested that most of such fecal fat is of endogenous origin. I believe that the phenomenon parallels the considerably increased amount of fecal nitrogen voided on "high residue" diets, such nitrogen, as McCance *et al.*[42, 43, 46] maintain, being mainly, if not entirely, of metabolic origin and not merely undigested protein nitrogen. Urbanized Bantu, substituting much maize by white bread, do *not* void such large amounts of fecal fat. The precise bearing of habitually large amounts of fat in the stools on the total body lipid picture is not known. Nor is it known whether the phenomenon described has any bearing on the tardy development of atherosclerosis in these people.

Calcium

It is widely believed that calcium absorption and bone calcification in man are controlled by the available radiation, by the amounts of vitamin D, calcium, and phytate phosphorus ingested, and by the calcium-phosphorus ratio. As already indicated, the high cereal diet of the Bantu is low in ingested vitamin D; with many local population groups the intake is virtually nil. The diet is also low in calcium—the average intake being about 250 to 400 mg. per diem—and has a very adverse calcium-phosphorus ratio. It is certainly high in phytate phosphorus, the intake varying (dependent on the extraction rate of the cereal) but ranging roughly from 1000 to 1500 mg. per diem. Therefore, according to current views the diet of these people, is poor in calcifying capacity. Certainly, there is plenty of sunlight, an average of 8 hours per diem in the Transvaal; but some authorities, such as Hess,[47] consider that a pigmented skin prejudices the production of vitamin D from radiation.

With this background, one would surely expect the stigmata of calcium deficiency to be apparent among these people. In fact, in no respect do the South African Bantu appear to be suffering specifically on account of their usual low intake of calcium.

The skeleton contains 99.5 per cent of the total body calcium. In my laboratory, studies on fifth ribs from Bantu and white subjects have revealed no significant difference between mean percentage composition values for infants and for adults.[48] Determinations of bone density of vertebral bodies (mineral matter per unit volume) have revealed, as with bone composition, a wider range of values than is usually thought to exist, but no significant difference between mean data for both races.[49] Furthermore, samples of vertebral body with marrow removed by refluxing with aqueous ethylene

diamine, when observed under the dissecting microscope with regard to mesh, regularity, and trabeculae, showed slight, although not invariable differences between bodies from both races. No bone examined could be regarded as atrophic, and all observations were in harmony with respective mineral density data.

Osteoporosis is not a feature of South African Bantu children or adults.

Concerning fractures, medical officers at hospitals attached to the Gold Mines (which employ about one third of one million short-term Bantu laborers) aver that the Bantu are not more liable to fracture their limbs than are white men under the same stress. These observers also maintain that, accompanying the more rapid callus formation in these people, a Bantu with a fractured leg, when it is healed, can stand on it much earlier than a white person with the same type of injury. These beliefs are only impressions, of course, but they do suggest that the Bantu skeleton, even if it contains, on a height basis, less *total* calcium compared to that of the white man, is not more vulnerable to physical stress or trauma.

Regarding clinical rickets, this disease is common in crowded urban areas in South Africa, just as it is under corresponding conditions at Ibadan in Nigeria,[50] Calcutta and Bombay in India,[51] and elsewhere. But the disease is often observed in breast-fed babies ingesting adequate calcium. Moreover, once the urban Bantu child has freedom of movement and need not be kept largely indoors (that is, after about two years of age), rickets is not seen—at a time when the calcium intake of the child is at its lowest throughout life.[52] In rural areas, however, where much less clothing is worn and where there is no overcrowding, obvious clinical rickets is seldom seen, although the character of the diet, at least in regard to ingested calcium and vitamin D, is much the same in both urban and rural areas.[53] This rarity of severe rickets observed when advantage is taken of available radiation is in agreement with reports from other observers in rural areas; indeed, certain pediatricians of repute almost deny having seen a case of obvious rickets in rural areas in the tropics and semitropics.[54, 55] No case of osteomalacia has been reported in a Bantu woman, pregnant or nonpregnant.

Generally speaking, the teeth of the Bantu, particularly the rural Bantu, are good. In one recent study carried out on children, about 90 per cent were found virtually free from caries; the reverse ratio is believed to obtain with local white children.[56] On the other hand, urbanization, with attendant changes in food habits (increased consumption of such foods as white bread and sugar) shows a deteriorating situation, thereby conforming to a pattern of experience common throughout the world.

Reasons have been given elsewhere for considering that the relationship between calcium intake and the rate of attainment of height or of ultimate height at maturity, is not proved.[57] In any case, studies by Kark and le Riche[58] indicate that the heights of Bantu children compare favorably with those of prewar Central School children of the same age group in Great Britain. Moreover, Bantu mine workers, on an average, are only an inch or so shorter than were British and American recruits in World War II.[57]

Serum calcium values,[59] speaking generally, are about 10 per cent less in

the Bantu than in white population groups. Examination of the information on this subject suggests that such values merely reflect a low habitual intake of the element, and are not indicative of low calcium stores.

Perhaps the key to the picture is afforded by the results of calcium balance observations carried out on Bantu prisoners consuming their high cereal, low calcium diet. I found percentage absorptions (apparent absorptions) to be higher and urinary excretions of calcium lower, than among white people on a much higher calcium intake. The combination of these two processes permits calcium equilibrium to be attained despite the low calcium intakes ingested. Other comparable studies demonstrating satisfactory adaptation to low calcium intakes have been enumerated and discussed by Mitchell.[60] In addition, there is the more recent study of Hegsted *et al.*[61]

The question of the "vulnerable" pregnant and lactating woman comes to the fore again. Prior to conception, body calcium of women may be regarded as approximating, roughly, 800 to 900 gm. The calcium content of the newborn infant is about 25 to 30 gm. The loss of calcium sustained by the mother when lactating for 6 months is about 35 to 40 gm., making a total loss of calcium of about 60 to 70 gm., that is, about 7 to 8 per cent of calcium reserves. The actual percentage loss, of course, is much smaller, bearing in mind that throughout the pregnancy and lactation period the mother is certainly absorbing *some* calcium from her diet. Now, a lactating cow can lose as much as 20 per cent of its total supply of calcium without giving rise to deleterious effects or without seriously interfering with milk production.[62] Therefore, on the basis of the information given, the loss of calcium sustained in pregnancy and thereafter cannot be regarded as of serious importance. The additional allowances of calcium usually recommended during pregnancy and lactation perhaps can be regarded as an insurance policy, although the precise risks involved are not altogether clear.

These data strongly indicate that the South African Bantu do not suffer specifically on account of their low calcium intake. Furthermore, the information given, by implication casts doubt on the importance still attached to the alleged deleterious effects of phytate-phosphorus and adverse calcium-phosphorus ratio in human nutrition. The clinical and pathological importance of both these factors, particularly the former, is open to considerable doubt.[63]

It may well be argued: it is conceded that what has been suggested may be valid for tropical and semitropical populations, but what of populations less favored by radiation? With regard to rickets, this argument may be met by citing the studies of Findley and Ferguson[64] on children in Glasgow, Scotland, and of Rustung[65] on children in Norway, where the chief controlling factor was found to be, not the diet consumed, but the regularity with which the child was taken outdoors. Reasons for doubting whether a low calcium intake has any serious relevance to the development of rickets in humans have already been expressed.[66]

Signs of a more realistic approach to the whole subject of calcium requirements and calcium deficiency stigmata are given by McLester and Darby,[67] also Goldsmith,[68] who refer to the lack of methods that permit detection of potential degrees of calcium deficiency: an observation difficult to harmonize

with the view often expressed in the past that calcium lack is a widely prevalent condition in the United States. More recently, Hegsted *et al.*[61] boldly averred that calcium deficiency does not occur in adult men. I go still further and raise the question: What is the evidence for *any* syndrome in man shown to arise specifically from calcium deficiency? Conversely, what syndrome in man has been shown to be remedied by calcium supplementation only? Surely, to recommend luxus allowances of a dietary constituent to protect against unspecified stigmata is a highly questionable procedure.

Iron

The Bantu of South Africa are characterized by an extremely high iron intake, often ten times or more the allowances of iron usually recommended. A population whose major source of calories is lightly milled cereal products normally ingests iron in excess of the recommended allowances. In published surveys on the local Bantu, calculated mean daily intakes range from 18 to 37 mg.[1-3] These people, however, derive additional amounts of iron from two extraneous sources: (1) dust and other such substances, and (2) iron derived from the utensils in which they prepare their food. The contribution from the first of these sources is highly variable, depending on the degree of care exercised in food storage, but it may reach one third of the calculated intake. The amount of adventitious iron derived from the second source is far more considerable, the principle of the phenomenon itself having been referred to in papers published by various overseas workers.[69] The chief utensil used by the Bantu is the heavy iron tripod "kaffir pot" (3-l. capacity, weight 4.5 kg.; 10-l., 13 kg.). Such vessels are to be found in almost every kraal in Southern Africa, over one million being sold annually. Iron kerosene cans (18 l., 4 gal.) are also used, especially in urban areas. Moreover, in large-scale cooking for Bantu workers (by industrial undertakings, for example), large iron vessels (100-l. capacity) are also employed. In the cooking of whole maize, maize and "kaffir corn" porridges, beans, vegetables, stew and greens, experimental observations, also determinations in such foodstuffs cooked by the Bantu themselves, reveal an uptake of iron as great as that contained in the parent foodstuffs.[70] Traditional foods of the Bantu, as noted earlier in this paper, include fermented cereal preparations. These foodstuffs, of *p*H 2 to 3, naturally take up much iron (as much as 10 times that in the raw food) from the preparation vessels. Briefly, our determinations have shown that the iron intake of the South African Bantu often exceeds 100 mg. per diem and, occasionally, reaches and even exceeds 200 mg. per diem.[70] It cannot be too strongly emphasized that it is iron vessels *plus* the particular diet of the Bantu that permit the ingestion of this excessively high iron intake; iron pots used in the dietary context of most Western populations will *not* give rise to a very high iron intake. Most of the adventitious iron is inorganic in character, and therefore readily available for absorption. What is the effect of such high iron intakes, which approximate the involuntary ingestion of several Blaud's pills daily?

Nearly two generations ago German workers such as Queckenstadt[71] had the impression that, with iron intakes much greater than those present in

everyday diets, excessive iron was retained, even by subjects not in need of iron. This impression received substantial confirmation from iron balance experiments carried out many years later and, despite the sources of error latent in such studies, they show unequivocally that an abnormally high iron intake is almost invariably accompanied by excessive absorption.[72-76] Less than 10 years ago, Dubach *et al.*[77] studied the absorption of radioiron by 10 normal subjects, total iron intakes being maintained at about 60 to 70 mg. per diem. The data given suggest that 9 of the 10 subjects absorbed a portion of iron that was not utilized in hemoglobin formation, this portion averaging 7 per cent of the iron intake. Unrequired iron was therefore "packed" into the body at the level of iron intake used. Now the only serious avenue of iron loss from the body is by hemorrhage. Briefly then, with iron intakes habitually high, as with the Bantu of Southern Africa, it would seem inevitable that occasional abnormal absorption and retention results, with intermittent deposition and slow accumulation or "overload" of the element occurring in the body.

Abnormal iron deposition or siderosis, is certainly widespread in the Bantu.[78-80] In Johannesburg, about two thirds of adults over 40 years examined at necropsy are affected; in Durban, according to Wainwright,[81] the figure is higher. The deposition in spleen, liver, and vertebral body marrow can and often does reach several grams per cent. The extent of the siderosis does not appear to be related to the cause of death, the condition appearing to be equally common in persons dying in hospital or from trauma.[80] In distribution, the spleen is most affected, then the liver; smaller concentrations are found in the kidney, but only traces in the pancreas, thyroid, heart, and blood vessels (aorta). The distribution thus differs very markedly from that in idiopathic hemochromatosis, particularly in relation to the pancreas, which, in hemochromatosis, is the organ suffering the greatest increase in iron concentration, that is, a mean of 100 times more than normal.[82] Furthermore, diabetes is very uncommon in Bantu siderosis (this is not the case in hemochromatosis) and, although cirrhosis is present in one quarter of severely siderotic livers, the association is far from being invariable.[79,80]

As would be expected, the high iron intake and the siderosis influence certain blood values. There is now a good deal of data, some published,[83, 83a, 84] more unpublished, indicating that iron deficiency anemia among these people is less common than among any other nonwhite population upon which data have been reported. This relationship is understandable, since Rath and Finch[85] have shown that body iron excess cannot co-exist with iron deficiency anemia. In this respect, Higginson,[86] at Baragwanath Non-European Hospital, Johannesburg, in a series of 1500 post-mortems and 500 liver biopsies extending over the last 7 years, has noted only one instance in which siderosis was present in a patient suffering from hypochromic anemia, but whose response to iron unfortunately was not known. Information obtained from this hospital, also from the chief non-European hospital in Durban, both relating to studies still in progress, indicates that incidences of primary iron deficiency anemia in Bantu adults are less than 0.2 per cent of admissions. This very low incidence stands out in startling contrast to a recent study on hospital

patients reported from India, [87] in which 63 per cent had a hemoglobin level of less than 6 gm. per cent, and 92 per cent a MCHC less than 32 per cent. Indeed, iron deficiency anemia would seem to be less common in hospitalized Bantu men and women than in numerous nonhospitalized groups of white subjects; for example, in a recent study on 4421 British Royal Air Force recruits,[88] anemia, chiefly of the iron deficiency type (93 per cent), was present in 1.2 per cent of subjects (criteria, Hb. $<$ 12 gm. per cent, MCHC $<$ 30).

Concerning the effect on another component, namely on serum iron, values are frequently elevated in both hospital and nonhospitalized Bantu populations, values occasionally exceeding those reported in hemochromatosis and transfusional siderosis.[83] There are, however, a number of anomalies in the serum iron picture of these people that require elucidation. In one collaborative study,[86] serum iron has been determined in adult subjects who have had liver biopsy undertaken for diagnostic purposes; we have found that excessive hemosiderin, when present in the biopsy sample, was associated with elevated serum iron. The actual level of the latter, however, did not correlate satisfactorily with the intensity of the siderosis. Further work on this problem is proceeding.

The primary cause of the siderosis, one has no doubt, is the habitually high iron intake. The incidence, age and sex affected, the morbid anatomical distribution of the element, and other characteristics are such as might be predicted to arise from habitual iron "overload." Obviously, the abnormal deposition in individuals is highly variable. Not only are there well-known individual differences in biological response, but differences obtain in regard to food preparation, dietary habits, and consumption levels; there are also such factors as blood destruction in malaria and slight hematuria in bilharziasis. Whether the particular pattern of the Bantu diet or malnutrition or undernutrition play any significant role is not yet known.

Finally, concerning the pathogenicity of siderosis, in experimentally induced siderosis in animals the production of pathological sequelae would seem to be almost uniformly negative (data summarized by Higginson *et al.*[80]). At the beginning of the century, authoritative physicians, such as Osler[89] were emphatic that the fact that prolonged iron therapy (extending sometimes for years) was not attended by ill effects. While that may well be valid for white populations, it would seem unjustifiable to assume that the siderosis in the Bantu likewise is innocuous. A liver damaged at weaning time conceivably is more sensitive to insults than one not similarly injured. Earlier in this paper, attention was drawn to the age trend correlation of siderosis and periportal fibrosis in Bantu adults. The extent of the information available on this association does not permit one to dogmatize, but whereas formerly one did not regard siderosis per se as pathological, now one is less sure, and much further work will be required to determine whether siderosis does or does not promote hepatic disease.

Niacin

Goldsmith and his co-workers[90] prepared wheat and maize (corn) diets containing equal, although relatively small, amounts of niacin and tryptophan,

4.7 and 190 mg. per diem, respectively; when fed to humans, only the maize diets produced pellagra. Among the South African Bantu, we have encountered another type of abnormality imposed by a predominantly maize diet, whereby Bantu mothers on a high maize diet have a mean breast milk niacin concentration (70/u gm. per cent), about half that of Bantu mothers on a Europeanized diet (150/u gm.), both diets having an approximately equal niacin content.[91] Whether the abnormality is due to the fact that a large proportion of the ingested niacin is "bound," or to supression of intestinal biosynthesis of the vitamin, or to other causes, is not known. As far as we are aware, there are no stigmata attached to this diminished intake of niacin by Bantu babies; in any case, the usual two thirds cow's-milk mixtures, which have been used successfully for many generations by white populations, contain *less* niacin than that found in the breast milk of Bantu mothers. A further point of interest is that, although Bantu mothers on a diet high in maize ingested only about half the amount of tryptophan present in the diet of Bantu mothers consuming a Europeanized diet, no significant difference was found in the mean tryptophan concentrations in the breast milk from both Bantu groups.

Vitamin C

Early pioneer work on vitamin C requirements was undertaken in Johannesburg by Fox,[92] who drew attention to the very small amounts of the vitamin that could prevent scurvy in Bantu mine workers. Fox's observations received confirmation from later comprehensive studies undertaken on white subjects.[93, 94] That scurvy certainly does occur among Bantu adults was adequately reported by Fox,[92] and two recent South African studies[95, 96] have added to our information on the subject. But the remarkable finding to which one desires to call attention is the extreme rarity of infantile scurvy in Bantu infants (4 cases in Johannesburg non-European hospitals in 5 years) weaned onto cereal "paps," despite the fact that the amount of the vitamin ingested often is virtually nil. The inexplicable fact is that we have nevertheless found usually satisfactory levels of vitamin C in the plasma of such subjects;[97] moreover, other local workers, for example Smit and Pretorius at Pretoria (personal communication) have noted appreciable amounts in the plasma of infants suffering from kwashiorkor. One is confident that large numbers of local Bantu infants receive less than one milligram of the vitamin per diem, yet their plasma levels are consistent with an ingestion of several milligrams per diem. It has accordingly been postulated that under the special conditions of "pap" intake by these Bantu babies, the possibility that there is an endogenous production of vitamin C cannot be excluded. Clearly the phenomenon occurs only in specific dietary contexts; Singh,[98] for example, has reported the occurrence of severe scurvy in Indian infants fed heated cow's milk.

Comment

Perhaps I should apologize for the fact that much of the information I have given refers to aspects other than those of diet and biochemistry as stated in

the title of this paper. However, if I had done otherwise, some of the lessons that I am hoping will be learned would have had reduced force.

It will be apparent that one of the main points before me is to emphasize the caution required before considering whether a diet is deficient in certain respects simply because habitual intakes are much lower than the usual allowances recommended. Absence, or at least the apparent absence, of relevant clinical and pathological stigmata in people accustomed to "deficient" intakes cannot but point to the strong probability that the particular recommended intakes are too high. Calcium would seem to be an outstanding example in this field. But the situation regarding animal protein calls for re-examination, as do the needs of pregnancy and lactation.

A further lesson to be learned concerns the biochemical picture (in blood, stools, urine, and breast milk) when it differs in Bantu and white subjects. The lesson, which local workers have thrust upon them, likewise concerns the caution needed before considering that this or that "abnormality" in the Bantu is pathological, when often the "abnormality" is the normal response in healthy persons elicited by the type of diet consumed. Lack of care in this respect would lead one to regard the enviably low blood lipid levels of these people as pathological, whereas precisely the reverse would seem to be the case.

Perhaps the greatest need in this whole subject is to elucidate the extent of the relationship between pattern of diet consumed, of metabolism imposed, and of pathology accruing. In the South African Bantu, the context permits, among other things, of a high rate of mortality and morbidity in the very young, and of a high incidence of liver pathology in later life. On the other hand, however, the context permits, *inter alia*, of a low incidence of certain diseases that, when taken together, exact a high toll of mortality and morbidity from Western populations, notably appendicitis, peptic ulcer, diabetes, cholelithiasis, atherosclerosis, and certain types of cancer. Those of us who are privileged to work in South Africa (although feeling the drawbacks attached to isolation) consider that the best contribution we can make to medical science is to find out all we can about the diet, biochemistry, metabolism, and pathology of its people, in the hope that useful leads of etiological value ultimately may be found, especially in regard to the Western "killers," heart disease and cancer.

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Some aspects of the nutrition and physique of Bantu communities

ALEXANDER R. P. WALKER
Human Biochemistry Research Unit, Council for Scientific and Industrial Research, and South African Institute for Medical Research, Johannesburg, South Africa

THE SUBJECT OF NUTRITION and physique, and the factors modifying them, is a vast one; hence, it will be possible to touch on only a very few aspects as they relate to Bantu communities. In this short paper it is proposed to mention a few points bearing on the physique and the nutrition of these people, to provide examples of the extent to which both aspects may be modified by local practices, and then briefly to discuss needs for the future. It will be understood that the writer primarily has in mind the Bantu resident in the Union of South Africa.

CERTAIN FEATURES OF BANTU PHYSIQUE

The term 'physique' has been defined as—'The physical or bodily structure, organisation, and development; the characteristic appearance or physical powers (of an individual or race)—a definition, it will be observed, which includes more than the aspects of weight and height.

GROWTH

Birth Weight and Prematurity

In 1944, Heynes and Hersch (19) collected single pregnancy records of 2298 labours of Bantu from 2 urban hospitals; 105 were stated to be unequivocally premature. The mean birth weight of the 2,193 babies was 6 lb. 12.4 oz.; 67–70% of babies weighed between 5¾–7¾ lb., and 17% weighed under 5½ lb. In another series (500) in which all mothers had antenatal assistance, mean birth weight was 7 lb. 4 oz. Among Whites of the same period, in comparison, a local series of 942 babies (excluding multiple births) had a mean birth weight of 7 lb. 8 oz., 5% weighing under 5½ lb. (30).

In rural and peri-urban areas, average birth weight varies from region to region, and appears to depend primarily on economic position. Thus, in one semi-rural Bantu township, where almost all adult males were regularly employed at a steel works, mean birth weight did not differ significantly from that of White babies born into homes of artisan workers in Johannesburg (unpublished observations).

Speaking generally, although the gap is narrowing, the birth weight of present day Bantu babies (rural and urban) is inferior to that of present day White babies; the Bantu figure approximates to that of babies born in England, Belgium and France at the turn of the century (39).

The much higher incidence of prematurity in the Bantu (and other non-white populations) may not be of significance in regard to their future well-being. It is well recognized in Central and Southern Africa that children, whose weight at birth by ordinary standards would cause them to be classed as premature, are often sturdy and active and can be reared without the special care that has to be lavished on White children of the same weight (14). In Johannesburg, Kahn *et al.* (24) found that the survival rate among 1,000 premature babies (almost exclusively under 4½ lb.) without the use of incubators, special feeding, etc., compared not unfavourably with that of overseas White premature infants.

Growth of Very Young Bantu Children

Jelliffe and Dean (23) have stated that "African children of poorer groups, living under both rural and town conditions, show the following quite abnormal growth, as judged by weight gain, in the early years of life: i) First 6 months of life: excellent growth with sufficient protein and calories supplied by a good flow of uncontaminated breast milk, while the child is protected from many infections by antibodies from the mother during pregnancy. ii) Second 6 months of life: fair growth, but breast milk no longer sufficient for child's needs of both protein and calories, and added foods (if any) usually mainly starchy carbohydrates, with little protein. iii) Second and third years of life: poor growth, or even no growth, or loss of weight for long periods, due to the low protein, mainly carbohydrate diets (starchy foods, sometimes small quantities of breast milk, a little added animal protein, such as

cow's milk, meat or fish), and to the numerous infections that occur (including diarrhoea, malaria, chest infection). During this stage, protein calorie malnutrition may occur. The 2 most common clinical forms are kwashiorkor and nutritional marasmus." Although written from Kampala, Uganda, statements similar to the above have emanated from the Congo (34), Rhodesia (15), and South Africa (42, 25). In contrast, among Bantu groups in a more favoured economic situation—as in the study of Kahn and Freedman (25) on children of Bantu nurses, sisters, and health visitors—growth data (both height and weight) during the period of the study (1–11 years) were found to tally with those of Iowa City standards of 'superior American children' (21).

Growth of Bantu School Children

Speaking generally, the height and weight pictures of Bantu children (rural and urban) almost invariably are inferior to those of contemporary White children, both local and overseas (36). Broadly, data combined from several studies suggest that current height of Bantu children is of the same order as children in the United States (18) at the turn of the century, and of British children cited in the Board of Education Study of Newman (37) in 1928. There are exceptions, of course; for example, in 1949, in an investigation of Welbourn (52) it was reported that the mean height of the Kampala Bantu children examined at 8 years was greater than that of local White children of the same age group, and incidentally, coming from very good homes. Bantu data for weight at various ages are slightly inferior to those of American and British children in the studies just cited. In comparison with poorer White children, for example those of Dundee and Glasgow (39) in 1920, mean weights of Bantu boys and girls at 13 years are superior. Although certain investigations suggest that increases in both height and weight in Bantu children have occurred within recent years, insufficient information is available to learn of the extent of such improvements.

Height and Weight at Maturity

The question of salient interest is, since Bantu children are both under height and weight, compared with White children, is growth merely delayed (not necessarily a deleterious happening), or does the slower growth prejudice both height and weight at maturity?

The following table indicates that the height of Bantu mine workers of 18–40 years (the group on which we have most information) is little inferior compared with corresponding Whites of the same age group.

Additionally, we have found smaller groups of rural Pedi and Tswana Bantu males, 20–40 years, to have mean heights of 65.5 and 66.25 in., respectively.

Regarding Bantu women, data are very inadequate. Small groups (100 or so) of Pedi and Tswana Bantu women, 20–45 years, were found to have mean heights of 60.5 and 61.5 in., respectively. The mean height of Dundee mothers in poor economic circumstances studied in 1920 was 60.94 in. (39). In the investigation of Kahn and Freedman (25) the mean height of the privileged group of Bantu mothers was 62.3 in., which is closely similar to that of Canadian women 20–40 years, namely, 62.7 in., reported by le Riche and Pett (32). Within the limitations of the studies cited, neither Bantu men nor women appear to be markedly inferior in height to White subjects.

TABLE 1. *Height of Male Population Groups at Maturity*

Observer	Population Group	No. Examined	Height, in.
Turner (46), 1910	South African Bantu		
	East Coast Bantu	1,337	66.5
	Transvaal Basuto	521	66.0
	Cape Province Bantu	680	66.25
Walker (48), 1954	East Coast Bantu	1,100	66.35
	Transvaal Basuto	650	66.25
	Cape Province Bantu	720	66.1
Carlson (4), 1942	United States Army recruits	800,000	67.5
Clements and Pickett (6), 1952	Scotsmen, National Service recruits	1,303	66.82

With both sexes and at all ages over 1 year, Bantu are inferior in weight in comparison to present day Whites. Moreover, in contrast to the latter, limited studies suggest that after 20 years weight does not increase significantly with age. In a recent series of Pedi males and females studied, of ages 20–80+ years, throughout the decades, males averaged approximately 127 ± 3 lb. and females 122 ± 2.5 lb. If the definition of leanness of McLester and Darby (33) be used, i.e. 15% underweight, then compared with Whites of similar height, the majority of Bantu children and Bantu men are 'lean'; it is very unusual to observe obesity in Bantu men. On the other hand, Bantu women appear to be 'lean' only after middle-age; obesity during the childbearing period is not uncommon, and is regarded by Bantu males as a desirable characteristic.

CERTAIN MILESTONES OF DEVELOPMENT OF BANTU

Psychomotor Development in Very Young Children

At Kampala, Uganda, Geber and Dean (14) reported that newborn Bantu children are at a more advanced state of development, judged by the criteria used, compared with normal White children. Much of the activity corresponds to an age of 4–8 weeks. In further studies on the psychomotor development of older Bantu children these workers found that up to the age of about 3 years development is usually in advance of White standards, the degree of advance being greatest in the youngest children. These findings are not unexpected, because observations on Bantu children in the first year of life have already shown that the accepted 'mile-stones' of development—raising the head, standing, walking, and so on—are passed at an earlier age than in White children. Unpublished ob-

servations of a similar character have been made on Bantu infants in Johannesburg.

Menarche

Kark (26) studied 1038 Bantu schoolgirls from 4 different rural areas in South Africa in relation to whether or not menstruation had commenced. In all groups investigated no girls had commenced menstruating before 13 years, when only 1 girl had started. At 15 years, 40.5% of the girls were having menses; at 16 the majority (80%) had started, while it was only at 19 years of age that all the girls were menstruating. Kark discussed certain possible factors influencing menarche age, namely, nutritional state, disease and climate; she considered physique and health to be important influencing factors, noting that in the groups studied the menarche occurred a year earlier in areas of improved compared with less satisfactory nutrition. The latter conclusion agrees with various data given by Mills (35) who noted, *inter alia*, that in Norway between 1868 and 1935 the mean age of onset declined from 16.1 to 14.5 years, a change undoubtedly related to improved standards of health and physique. In a recent unpublished study on 1,000 girls in a Johannesburg Bantu township, Oettle and Higginson obtained a mean figure of 14.8 years. A current figure for British girls is 13.5 years (54). To throw further light on the possibilities of using this criterion (time of onset of menses) as an index of nutritional state, Oettle has initiated large scale studies on Bantu schoolgirls in several regions.

PHYSIQUE AND PHYSICAL PERFORMANCE

Physical Prowess at Work

In tribal life, it is usual for females to do the harder work—cultivating, weeding, fetching of water and fuel, 'stamping' or grinding of cereals, and other household tasks. Men are concerned primarily with hut building, overseeing of the cattle, ploughing and sowing. Although Bantu males pursue a more active life than White males, the former are not characteristically hard workers. Nevertheless, under conditions where heavy manual work is required, as for example with Bantu mine workers, their capacity, even without training, appears to be in advance of that of similar White workers (Personal communication, Dr. C. J. Wyndham, Director, Applied Physiology Unit, Chamber of Mines).

Motor Fitness

Schoolchildren. Le Riche *et al.* (31) carried out studies using the Harvard Step Test (a test of physical performance) on Bantu boys at a local institution for young delinquents. They found 90% to be in the "good, excellent, or superior" classes in comparison with 30% noted in a corresponding study on American private school boys. We have carried out further similar studies on rural Bantu children, reaching the same conclusion. A correlation was found between Step Test performance and the height and weight pictures in different rural Bantu schools.

Bantu young men. Working with Bantu mine workers, Drs. Morrison and Strydom (personal communication) found that performances of mining recruits compared with White students entering the University of Illinois (8) were closely similar. The following mean scores for Bantu and Whites were obtained: 'Chinning,' 8.55 and 9.81; 'dipping,' 7.79 and 10.67; running the mile, 7.17 and 7.11 minutes; and for 'push-ups,' 15.62 and 16.49, respectively.

Older subjects. In an unpublished study, Dr. P. J. Kloppers and associated workers have investigated Harvard Step Test performance by Bantu and White prisoners (long-term) at Pretoria Gaol. Habitual activity in the racial groups differed little, yet the Bantu showed significant superiority in performance.

FACTORS INFLUENCING PHYSIQUE

Genetic Factors

The extent by which genetic factors influence growth and ultimate height has occupied much attention in many countries. In an early careful study on *Poverty, Nutrition and Growth* (39), published in 1926, the following quotation appears. "The persistence of racial characteristics has been interestingly shown in the report of the Medical Department of the U. S. Army in the World War (1921), where statistics relating to measurements of draft recruits in the U. S. Army showed racial differences as to height and body build clearly marked in the inhabitants of the country, the Scot-American being tallest of the 8 European races listed, with an average height of 67.93 in., while the Italian-American had an average height of 65.03 in. Racial variation is also shown in other measurements."

In Southern Africa there are very tall Bantu groups, like the Watussi of Belgian Congo. There are the very short statured Bushmen of the Kalahari Desert, a non-Bantu African group who were dwelling in the South before the general Bantu invasion in the 17th century. There are numerous tribal groups with intermediate statures, but the extent to which such are influenced by genetics has not been studied. Investigations like those on Japanese children dwelling in the United States (17), and on privileged South African Bantu groups, as in the study of Kahn and Freedman (25) suggest, however, that the genetic factor is not of overriding importance in the determination of rate of attainment of height.

Nutritional Factors

The food resources of rural Bantu communities depend on the agricultural potentiality of their land (terrain, soil, rainfall, temperature, altitude, etc.), the presence or absence of crop and animal parasites, as

well as on the providence and intelligence of the peoples themselves. In urban areas, the diet consumed (especially the type of foods) depends primarily on economic position. Obviously, it is very difficult to generalise, since the nutritional situation differs so much from region to region, and even within the same region. But very broadly, where cereals (maize, sorghum or 'kaffir corn,' millet) are the main source of calories, as in South Africa, the energy value of the diet is unlikely to be grossly deficient, except among the very young. Gross protein may not be seriously low, but the intake of animal protein certainly is low. Further north, where cassava, sweet potatoes, plantains, and manioc, are staple sources of calories, the nutritional position is inferior to that where cereal consumption predominates. The nutritional situations in Central and Southern Africa in regard to the young are well discussed in *Kwashiorkor in Africa* (3), and, in so far as South Africa is concerned, in the series of papers by Fox (12, 13) on 'Nutritional foundations of agriculture'. Regarding other features of the diet, the intake of fat is low almost invariably. The intake of certain mineral salts and vitamins is influenced to a large extent by the amount of green leaves (morogo, m'fino) and vegetables consumed. As already indicated, diet may differ markedly in near-by regions, e.g. among the Masai and Kikuyu (38) of Kenya, and among Shangaans in Mocambique and those dwelling on the Highveld beyond the ridge of the Drakensberg. In centres of population, some 'westernization' of diet and manner of life is occurring; certain of the changes involved are mentioned later. It should be added that low intakes of certain nutrients, e.g. calcium by the general population (50) and vitamin C by babies (1), do not appear to be accompanied by demonstrable stigmata.

Zymotic Factors: Parasitic Infestation

In southern Africa, there are regions where parasitic infestations—blood borne, helminthic and protozoal—are endemic. Understandably, their presence and severity have a strong influence on nutritional state and physique. Malaria and trypanosomiasis no longer are public health problems in the Union, but west in Mocambique, and northwards in the Rhodesias, Nyasaland, and Kenya, these and like diseases aggravate the ill-health picture when due to unsatisfactory nutrition. Bilharzia is rife in many regions, but apparently the ill effects are less marked in the Union compared with neighbouring territories. The same applies to ancylostomiasis (hookworm) and other helminthic infestations, which appear to be much greater problems in the coastal regions compared with the inland Highveld. Here again, the parasite situation can differ markedly in near-by regions. In studies on certain Bantu school children in Western Transvaal almost three quarters were found to be free from helminthic infestation. But 50 miles or so further west almost all children studied were parasitized, some heavily so. (Personal communication, Dr. J. J. Theron, National Nutrition Research Institute.)

EXAMPLES OF THE INFLUENCE OF LOCAL FACTORS AND PRACTICES ON NUTRITION AND PHYSIQUE

Babies

The following examples indicate how prejudicial local practices may be in relation to infant nutrition. In earlier days, according to Keen (27), 30% of Swazi babies died during their first year, the majority succumbing during the first month. There were many possible causes of this—malaria, syphilis, bad hygiene, ignorance, etc., but Keen stated that the main cause was the terrible custom among the Swazi that a new born baby was not put to the breast until the umbilical cord had fallen off. This takes about 5 days, and during that time the baby is fed on soft maize meal porridge, made into a very thin paste and just pushed into the baby's mouth. As a second example, many Zulu (22) mothers believe that their colostrum is not healthy for the baby, so they treat their breasts by squeezing them and applying hot fomentations for 2–3 days, or even as late as 5–6 days, before putting the baby to the breast. During this period weak maize paps are given, with or without sugar,—with understandable deleterious effects.

Children

The following study illustrates how influential a little known tribal practice may be on the growth of each sex of school children.

Over the course of a year, Keen (27) made observations on groups of Swazi school children (boys and girls) at boarding and day schools. The boarding school group grew as expected. However, although the day girls grew regularly, the day boys gained practically no weight during term time. The tremendous difference between the day boys and girls was investigated. On referring the facts to the principal, it was noted that the day girls brought food with them, yet very few of the day boys had anything to eat at midday. Ultimately, it transpired that the Swazi male is not allowed to carry food, this being the prerogative of the female. The Swazi boy would rather go hungry all day than degrade himself by carrying food to school. Here therefore was a little known Swazi custom which obviously accounted for the difference in growth rate between the boys and girls.

Girls and Pregnant and Lactating Women

There are numerous reports bearing on abstinence from valuable foods by girls, pregnant and lactating women, due to tribal customs. The young adolescent Zulu girl (22) is forbidden to consume eggs, since it is believed that females (especially young adults) become excessively fond of men as a result of consumption of this foodstuff. Eggs, moreover, are believed to lead to

barrenness. Among the Mashona of Southern Rhodesia, Jali (22) refers to certain tribes among whom mothers throughout their pregnancies go without milk, this foodstuff being taboo.

The Effects of Urbanisation

The effects of urbanisation are widespread in their ramifications. Certainly, medical treatment and hospitalisation facilities are far in advance of such in rural areas, and urban Bantu are becoming increasingly hospital conscious. On the other hand, tribal discipline is greatly weakened, and promiscuity and venereal disease, relatively rare in most country regions, increase markedly with urbanisation. Concerning nutrition, whole grain or high extraction cereals progressively give way to white bread and sugar, a pattern all too familiar to those acquainted with the impact of White civilisation on backward peoples (White and non-White). The whole subject is so enormous that the relevant ramifications on nutrition and physique can scarcely be touched upon in a short space. However, 2 examples of changes will be given. *1*) It is usual for Bantu mothers to produce breast milk adequate in amount and satisfactory in composition (47). In urban areas, however, the practice is being replaced by the use of proprietary products, prepared almost invariably in too dilute a manner (49). Even in Central Africa, Watt (51) states "Unfortunately dried milk preparations, widely advertised by press and hoardings, are gaining an unwelcome foothold." Unless prepared correctly, such preparations cannot but favour the development of infant malnutrition or even semistarvation. *2*) In rural areas, Bantu infants wear the minimum of clothing, and hence are exposed to abundant radiation. In such regions, many able clinicians of long standing have yet to see severe rickets. On the other hand, the crowded conditions in urban townships together with overclothing favour the occurrence of rickets, which is very common and often severe (10). This same situation prevails in similar centres of population elsewhere (50), e.g. in India, China, etc., and until recent decades, western cities such as Glasgow (11).

DISCUSSION

From the foregoing, several points seem apparent. Although the position differs somewhat from region to region, South African Bantu babies are lighter at birth, and grow slower than White children. Ultimate height for males and females is not markedly inferior to that of Whites. Weight, however, is lower in all groups, especially in males and females after middle age. In psychomotor development, new born Bantu babies are precocious, this feature extending into the 3rd year. In Harvard Step Test performance, studies indicate that the Bantu (children, young men, older men) are superior to Whites. Bantu girls are significantly later in starting their menses, although the gap between their onset and that of White girls is decreasing. In pregnancy, Bantu mothers appear to fare at least as well, and almost invariably they lactate better than White mothers. Yet, among these people intakes of nutrients, in terms of orthodox recommended allowances, are inadequate, sometimes grossly so; zymotic diseases, of varying intensities, exact their toll; moreover, numerous tribal practices can have a deleterious influence on nutritional state and physique.

What then of the future? What are we to seek to do? For the philosophy of proceeding slowly, various points have been considered from time to time.

Among Bantu young children,—the syndrome which causes perhaps most anxiety in relation to mortality and morbidity is kwashiorkor. Nevertheless, although long term studies are few, there appears to be no evidence that patients recovering are *ipso facto* seriously stigmatised in later life (43, 53). Furthermore, in this connection, it would also appear that slower growth in older children due to temporary adverse nutritional conditions (as with German (2) and French (44) children during the last 2 wars) does not necessarily prejudice future growth once the situation improves. Cathcart (5), quoting an earlier authority, once asked "Should we aim, as some enthusiasts would have us do, at feeding children in such a way as to produce the maximum growth and development of which each child is capable? If we succeed in this are we sure that we have benefited the child? Does maximum growth make for health and longevity? There is certainly some evidence that it does not. . . ."

Carlson (4) stated that of the first 800,000 U. S. A. selectees in 1941, the mean height was 67.5 in., the same as for the 1917–1918 draftees; but the 1941 recruits averaged 8 lb. heavier. During that intervening period some have feared that physique deteriorated (7, 40). The question arises, was that gain in weight essentially beneficial?

Keys (29) has pointed out "at the same height and age, Britons tend to be lighter than Americans, and the age increment in weight is smaller. In Japan, not only is the relative weight smaller, but the age increment in weight is much smaller than our own. A continuous rise in body weight with age, such as is the situation in the United States, is not inevitable. Among relatively primitive people on islands in the China Sea, there is no increase of average body weight after twenty-five".

These points suggest that the provision of additional calories to the South African Bantu population from school age onwards may not be wholly rewarding; they counsel a policy of cautious change. Also to be borne in mind is the fact that the Bantu pattern of diet and manner of life are associated, *inter alia*, with a relatively low mortality rate from cancer (20), and an extremely low mortality rate from coronary heart disease (50). If possible, our well meant desires to help must not simultaneously promote increases in these and other diseases which together exact such a fearful toll of lives among western populations.

But as against this detached, conservative, and in some ways inhuman approach, it must be faced that in comparisons of vital statistics (infantile mortality rate, tuberculosis mortality rate, expectation of life, etc.) the Bantu are considerably inferior to Whites. In a paper of this type, however, it would not be appropriate to seek to elucidate and apportion blame to the various factors, nutritional and non-nutritional, responsible for the adverse aspects of the Bantu health picture, a picture, moreover, which in many respects is common to the majority of the world's population today. There is only room to bring to the fore the salient point which the writer desires to emphasize, namely, that with increased spending power and other relevant alleviating measures, it is imperative to increase the education of these people in the widest sense. It is not so much literacy that is at issue, since the great majority of these people already are literate; it is the aspects of education which will inculcate understanding, self-reliance, and responsibility. What is in mind will not be exemplified.

An increase in spending power will afford amelioration only if a portion of the increase in money is spent wisely. Thus, additional food may not be entirely beneficial if it consists wholly of white bread, sugar, soft drinks, sweets, etc., such being the pattern of change now being observed in centres of population in the Union. The obtaining of dried milk (whether purchased at retail price, reduced cost, or gratuitous) will not be of maximum value in the post weaning period of Bantu infants if mothers almost invariably prepare the foodstuff for consumption in too dilute a manner, as is the case at present. In this connection it will be remembered how often it has been reported that in many regions where kwashiorkor is common the cause does not stem primarily from poverty, but from ignorance and apathy. The Bantu child after weaning, in contrast to the White child, has no priority at meal time in the family circle. Numerous other examples of this type could be given. In brief, as Keen (28) has stated, "without an intimate knowledge of Bantu psychology and tribal customs, our efforts in the nutritional field are doomed to failure. . . . As far as the rural Bantu is concerned, the difficulties will not be overcome by animal experiments, laboratory work, or dietetic calculations, but only by a vast social and educational revolution." But it is not only in regard to nutritional matters that education is important. In the field of medical treatment, for example, Keen (28) relates the case of 1 of his patients who was 'bewitched.' Despite batteries of diagnostic tests and observations, nothing unequivocally wrong could be found. Ultimately, the young man went to a celebrated witch doctor in Natal, by whom he became 'de-witched', and then quickly gained health and strength. Although these occurrences are becoming less common, at least in urban areas, their elimination will not be accomplished quickly. Even in the field of medical research, one rapidly comes up against tribal inhibitions and taboos. One manifestation is reluctance to give samples of blood and stools (although not breast milk) for analysis. We have often had to give half a dollar for a little blood from non-hospitalised people from whom we particularly wanted samples. But most dramatic of all appears to be the reluctance to part with excreta, for fear of how its fate may affect the person's future. At this Institute, there are over 200 Bantu helpers. At one time the writer was seeking to carry out studies on the faecal lipids of these people. Yet even with incentives of half a dollar per stool and half a dollar reward to the 'boss boy' in charge, only 10 stools were obtained.

It would seem inescapable that all our endeavours in relation to practical improvements in physique and nutrition, in relation to reduction of zymotic disease (which Platt (41) regards as the more important task) and in kindred health matters, will be stultified, unless equally intense endeavours be made to educate the Bantu in the respects described. What is being emphasized, obviously, is far from new. It has been the burden of recommendations in numerous conferences and symposia bearing on the whole subject.

It will be understood, of course, that irrespective of changes in spending power, in health education, etc., several activities by both State and community are pressing on simultaneously, which when taken together and given time cannot but contribute to improvements in health. Thus, there are control measures against malaria, bilharzia, etc., and the provision of inoculations against smallpox, diphtheria, and polio; there is improved housing in urban areas, increased hospital services (especially in regard to tuberculosis) and antenatal and child welfare clinics; there is the subsidisation of the price of cereal foodstuffs, and the provision of certain foods at low cost (e.g. dried milk); moreover, the question of enrichment of cereal products is under very active investigation (16, 36).

It must be reiterated, however, that the value of all these measures will be limited unless the education of these people in health matters be improved, and their providence stimulated.

SUMMARY

Information has been given on certain aspects bearing on the physique of the Bantu—birth weight (and prematurity), growth of children, height and weight at maturity; certain milestones of development (psychomotor development, onset of menses), and motor fitness (prowess at work, physical performance). This was followed by brief general information on the factors likely to influence this picture (genetic, nutritional, zymotic disease, local tribal practices).

While the physique picture of the Bantu does not give cause for serious concern, the vital statistics situation is far from satisfactory. It has been suggested that the aspect most deserving of attention is the educational aspect in its broadest sense, without which the best ameliorative efforts by State and community will fall far short of their potential effectiveness.

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GROWTH, NUTRITION AND PARASITISM

SIR,—It is regarded as axiomatic that growth is dependent on nutritional state, and that the latter is likely to be prejudiced by parasites, particularly if infestations be severe. Under conditions of severe dietary inadequacy and of intensive parasitization, undoubtedly such cannot but fail to prejudice gain in weight and rate of attainment of height. However, under less severe conditions, anomalies occur. For some years at this centre we have been endeavouring to throw light on the handicap imposed by schistosomiasis in Bantu children, and for this purpose have been studying three schools near by each other in the Rustenburg Native Reserve region in Western Transvaal: (1) Tweedepoort, with 100 per cent. *S. haematobium* infestation, where the water consumed comes from the River Hex; (2) Tleseng, virtually with no schistosomiasis, the source of water being shallow wells; and (3) Kana School, where there is about 50 per cent. infestation. The assessment situation is simplified by the fact that about 80 per cent. of stools from each school are free from helminths. Exhaustive long-term observations have failed to reveal which school population is handicapped, or which particular child is at a disadvantage on account of bilharzia, observations including those relating to growth measurements, clinical state, haematology and biochemistry, motor fitness (including Harvard step test), and educational prowess. Indeed, the Gilbertian situation is such that, broadly, the children with schistosomiasis have been found to be somewhat superior to those without, in respect of the step-test performance and educational ability. It might be conjectured, of course, (i) that the bilharzial infestation is not severe, and (ii) that habitual diet and nutritional state are sufficient to mask any disability from the disease. Nevertheless, comparative observations in different parts of Southern Africa have indicated that, in so far as intensity of ova in the urine also the proportion of subjects with gross haematuria are concerned, the infestation at Rustenburg is relatively severe; moreover, although the general diet is not obviously inadequate, it is certainly low in animal protein foods, vegetables and fruit. In view of these rather negative findings, it was thought worth while to conduct corresponding observations in another part of the country. In association with Dr. R. J. Pitchford, Head of the C.S.I.R. Bilharzia Research Unit at Nelspruit, it was resolved to study Bantu children in the Crocodile River Valley in the Eastern Transvaal lowveld. In that valley, children have nearly 100 per cent. infestation with *S. haematobium* and about 75 per cent. infestation with *S. mansoni*, together with less frequent infestations of hookworm and certain other helminths. Our observations will be reported in detail elsewhere, but the paradoxical finding which we wish to draw attention to, is that the mean weight and height of the Bantu boys and girls of the three schools examined (Hectorspruit, Minty, and Komatipoort) are far higher than corresponding values noted at Rustenburg; for the 15-year-old children, the differences are about 15-20 lb. weight and 2-3 ins. in height. The mean height of the adult males in the two regions does not differ significantly. The state of growth of the Crocodile Valley children probably is nearer to that of corresponding South African whites than any other Bantu group; indeed, the Bantu growth data are almost identical to those reported for London County Council School children in 1948. Yet the diet of these lowveld Bantu, apart from a much higher consumption of vegetables and fruit, is substantially the same as that of the Rustenburg schoolchildren.

Many anomalies such as the above are encountered by those working among under-developed populations. Thus, Welbourn (*E. Afr. med. J.*, **26**, 391, 1949) has reported the superior growth of Kampala African children of 8 years compared with that of local European children coming from good homes, despite the fact that upper respiratory infection, malaria and hookworm were more common among the African group. Other anomalies recently have been pointed out (Walker, A. R. P., *Nutr. Revs.*, **19**, 257, 1961).

The foregoing information is given simply to illustrate the difficulties confronting the making of a precise assessment of disability from parasitism on state of nutrition or general health. It is our intention to characterize the Crocodile Valley Bantu as carefully as possible in order to assess the maximum adverse factors operating, yet still compatible with good growth.

We are, etc.,
ALEXANDER R. P. WALKER,
COLLEEN DE LACY.

C.S.I.R. Human Biochemistry Research Unit,
South African Institute for Medical Research,
Johannesburg.
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THE CHANGING PATTERN OF GROWTH AND OTHER PARAMETERS IN SOUTH AFRICAN BANTU CHILDREN

Workers in South Africa are particularly fortunate in having four ethnic groups available for study, - Whites, Bantu, "Coloured" (Eur-Africans), and Indians. This wealth of human material is further augmented by the fact that in each population, there are sections which differ widely in socio-economic state, diet, activity, occupation, and in other respects. In the three Non-White population groups, the value of the situation is still further augmented on account of their exposure and reaction to the impact of increasing westernization. This great diversity of material therefore provides unusually valuable opportunities for the throwing of additional light on a variety of subjects.

One aspect of research which we have been pursuing concerns the changes observed in Bantu children in transition, - from rural to urban centres, primitiveness to sophistication, indigency to relatively comfortable circumstances. While full details of these investigations will be published elsewhere, it has been thought worthwhile to mention briefly some of the changes which we have noted, which indicate that the tempo of changes occurring in these young Bantu is perhaps more rapid that is generally appreciated.

Regarding weight and height, we have found that Bantu boys and girls at Secondary Schools have much the same mean values as the poorer moiety of present day London Council School children. Urban more privileged Bantu children are as much as 25 lb. heavier and 3 inches taller than the poorer section of their rural counterparts. Even among the latter, however, there have been very significant gains in weight and height in observations made over the last ten years. In relation to skin-folds (triceps, scapula, iliac, umbilicus), we have found that all groups of Bantu boys studied have mean values consistently lower than those of White boys of the same age. On the other hand, Bantu girls at urban

Higher Primary Schools have values closely similar to those of White girls; furthermore, Bantu girls at urban Secondary Schools have been found to have mean values significantly greater than those of contemporary White girls. Investigations have revealed that mean age at menarche in the poorer rural girls is approximately 15.0 years; whereas, the mean age for girls in urban Secondary Schools is about 13.2 - 13.6 years, i.e. much the same as current figures for British girls. We have noted graded changes in serum gamma globulin concentration. The most privileged of urban Bantu children still have values markedly greater than mean values found in White children; nevertheless, we have found a fall in this parameter with rise in socio-economic state in both urban and rural children. Mean values for urinary nitrogen excretion in better class urban Bantu children are much the same as values reported for White children; poorer rural Bantu children have lower mean values, although not as low as average values for Indian children in rural India. In respect of serum cholesterol, we have found step-wise increases in this component with rise in socio-economic state, both in rural and urban areas; mean values in urban Secondary School post adolescent children closely approach those of White children. Iron deficiency anaemia has been found to be rare in all groups studied; better class children have higher mean haematological values than the poorer groups. In respect of blood pressures, we have found a slight, although significant, rise from rural to urban areas; girls have been found to have higher mean values than boys.

The foregoing information is sufficient to illustrate the magnitude of the altering pattern of dietary, anthropometric, biochemical, and other changes now affecting the younger Bantu. While there is much that is commendable in these changes, caution must be exercised before considering that every change towards norms in White children is wholly beneficial. There is little doubt that the ponderal index (weight / height) in at least privileged Bantu girls will shortly exceed values in White girls. It is possible that the same trend may obtain with regard to blood pressure. Among adult urban Bantu, the tendancy toward overweight and hypertension with increasing urbanisation

(also noticed among other emerging populations) has been commented upon elsewhere.[1] A rise in blood cholesterol levels to values approaching those of Europeans is scarcely gratifying, bearing in mind current hypotheses on the pathogenesis of arteriosclerotic heart disease.

While certain of the trends present or anticipated are regrettable, they cannot be regarded as being other than inevitable. In a previous publication on some thoughts on the future health of the South African Bantu,[2] the fact was underlined that the Bantu are now moving from a context of falling mortality from deficiency and infectious diseases, to an expected rising mortality from diseases of prosperity and nutritional excess. This has been the experience of all other emerging populations. The pattern of changes evinced by the Bantu will be the pattern followed by other African populations before the end of the century.

Alexander R.P.Walker,

B.D.Richardson,

A.Nurse,

B.F.Walker.

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THE NUTRITIONAL STATE OF SOUTH AFRICAN CHILD POPULATION GROUPS AS REFLECTED BY HEIGHT, WEIGHT, AND NITROGEN PARTITION IN THE URINE

ALEXANDER R. P. WALKER, *C.S.I.R. Human Biochemistry Research Unit, South African Institute for Medical Research, Johannesburg*

In South Africa there are Whites, Coloureds, Indians, and Bantu. Certainly among the last 3 groups there are many who are undernourished or malnourished. While the primary cause is lack of nourishing food, the part played by infections must be kept in mind. Thus, among at least the non-White populations, a high infant mortality from gastro-intestinal infections may prevail even when infants are wholly breast fed.[1] In older children, too, infections may be very common. Thus, among 2 Bantu school-children groups studied in rural and peri-urban areas, serial examination of stools throughout the period of a year revealed that 3 of every 4 children had evidence of typhoid or dysentery infections.[2,3] In addition, infestations by helminths are common and intense in certain regional populations.[4] Apart from handicaps from poor nutrition and infections, deleterious effects may result from overcrowding, long distances to be travelled to school or to work, and other environmental factors. Nevertheless, there is no doubt that quantity and quality of food consumed are of decisive importance in the nutritional state.

There are many reasons why we require knowledge of the nutritional state of population groups:

1. The first reason is for public-health purposes. This requires no amplification.

2. In all ethnic groups the standard of living has risen. The 'Poor White' problem is far less serious now than 30 years ago, the time of writing of the Carnegie Report.[5,6] Turning to more privileged communities, there is evidence that Pretoria White children are now taller and heavier than corresponding children studied 20 years ago.[7,8] Among the Bantu, elevation of socio-economic status is reflected by an increasing rate of growth found in certain rural school-child populations observed over the past 10 years;[6] moreover, it has been shown recently that growth among better-class urban groups is similar to that of Whites.[9] Associated with these changes, particularly among the Bantu, biochemical and metabolic patterns are also changing; so too are patterns of disease. Reversal of the serum albumin/globulin ratio is encountered less frequently in present urban Bantu compared with the situation prevailing 10 years ago.[6] Observations indicate a progressive rise in serum cholesterol when comparing rural Bantu (120 - 150 mg.%), general urban Bantu (160 - 180 mg.%), and 'sophisticated' urban Bantu (190 - 220 mg.%); this reflects increased intakes of calories and fat in urban residents.[6,10] Regarding conditions or diseases associated with increasing privilege, there is evidence that obesity is now commoner amongst 'Poor Whites'[5,6] and among urban Bantu.[5,11] Diabetes in the latter is probably increasing,[12] and coronary heart disease, although still very rare, appears to be becoming slightly commoner.[13] Numerous other items of relevant information could be adduced. The salient point is that there is a dynamic state of change in South African populations, especially among the Bantu, in regard to diet, growth, literacy, socio-economic status, intensity of urbanization, and other factors. If medical science is to learn worth-while lessons from these changes, with regard to epidemiology, aetiology, metabolism, etc., then it is imperative to know the rate of change of the general nutritional state of constituent population groups.

3. A third reason for this need (actually an extension of the second reason) may be illustrated from problems at present confronting this unit:

(*a*) In seeking to obtain information about the milestones of development in the young in the different ethnic groups, one aspect we are enquiring into is the mean age of onset of menarche. When making interracial comparisons it is obviously necessary to know the general state of nutrition of the groups under study.

(*b*) In endeavours to throw light on the handicap to health imposed by parasitism, it is necessary when making comparative observations to know of the nutritional state of the populations showing different degrees of parasitism.[14,15]

(*c*) Current research on the aetiology of osteoporosis in Whites suggests that in a large proportion of cases a low intake of calcium may be chiefly responsible.[16,17] Since the Bantu are used to a much lower calcium intake than Whites, it might be expected that they would evince more osteoporosis. To throw light on the calcium status of these people, we are, on the recommendation of Nordin,[18] determining the phosphorus excretion index and the urinary calcium/creatinine ratio in different groups of Bantu and other ethnic groups. Understandably, the nutritional state of subjects must be determined.

(*d*) While there is little doubt that the primary aetiological factor in siderosis in the Bantu is their intermittent high iron intake,[19,20] it is necessary to determine whether malnutrition *per se* plays a role.[21] Hence, it is essential to make an assessment of the nutritional state of subjects upon whom serum-iron and other data are being obtained.

(*e*) In trying to learn of the bearing of hormonal activity on atherosclerosis and coronary heart disease, we must have knowledge, *inter alia*, of the androgen-oestrogen excretion patterns in the different population groups.[22,23] Here again, the need to assess the state of nutrition, or, in certain groups, the extent of 'Westernization', is understandable.

For the above and for many other investigations that could be cited, it is necessary to have the means of learning of the nutritional state of groups of people and of individuals, of children and of adults.

How may nutritional status be measured? To provide

adequate information it is necessary to know (1) habitual quantity and quality of food components consumed; (2) weight, height, skinfold thickness, and clinical deficiency stigmata; (3) biochemistry of blood and excreta.

Along these avenues of approach, however, full information is very difficult to obtain. Estimates of the intakes of specific nutrients for large numbers of subjects are skilled and costly procedures to carry out. The assessment of mild clinical deficiency stigmata is subject to considerable observer bias; some authorities have even queried whether the results are worth while.[24] Many of the biochemical methods are complex and time-consuming and subject, moreover, to differences of interpretation. What really is required for the specific purposes just detailed is a relatively simple test or series of tests which will provide a broad indication whether population groups or individuals, particularly the young, are poorly, moderately, or well nourished.

Of all nutrients, protein is most influential in determining nutritional state, and the amount of nitrogen excreted *per diem* in the urine is believed to be a good reflection of protein intake.[25] But to obtain accurate 24-hour urine samples is difficult, even under hospital conditions; collections from non-hospital people present a much greater task. Furthermore, while the excretion figure as an index appears valid for adults, it is somewhat less reliable for children.[25]

An associated approach is based on the observation of Folin[26] that with an intake of protein nitrogen of 16 G. *per diem* (i.e. about 100 G. of protein), 87·5% of the total nitrogen in the urine is excreted as urea. This finding has been developed by Platt and Heard,[27] who consider that, in a morning sample of urine, urea nitrogen plus ammonia nitrogen as a percentage of total nitrogen provides a rough but reliable index of nitrogen intake and hence of protein intake. The proportion may be as low as 30% in severely malnourished subjects, but reaches 90% or more on a high-protein diet.[27,28] Arroyave[25,29] considers that urea nitrogen/total nitrogen percentage is equally satisfactory, but maintains that the examination should be carried out on fasting samples of urine. Luyken and Luyken-Koning,[30] however, have found the effect of a meal to be slight. Arroyave[29] also considers that since creatinine, for practical purposes, is not affected directly by variations in protein intake, the amount of urea excreted can be expressed per unit of creatinine, in the same manner as is customary for the water-soluble vitamins or their metabolites; this index may be more sensitive for the purpose in mind than the urea nitrogen/total nitrogen percentage.

The two topics for study which primarily stimulated our interest in this subject are those listed above in this column as (1) and (2). In the present investigation, which is preliminary in character, we have concentrated upon them, and have determined the nitrogen partition percentage and the urea/creatinine ratio in the urine, and the weight, height, and certain other criteria in a number of different groups of school children (White, Indian and Bantu).

SUBJECTS AND METHODS

The subjects ranged from 14 to 17 years old, and included the following groups (see table):

Whites. 38 boys in a rural high school in the Transvaal.

Indians. (1) 43 boys in an urban high school of good socio-economic position, predominantly Moslem. (2) 41 boys in an urban high school of good socio-economic position, predominantly Hindu. (3) 45 boys in an urban school of poor economic status, predominantly Hindu. (4) 30 boys in a rural school, poor, and mainly Hindu. All these schools were in Natal. Studies on Indian girls were not considered expedient by the teachers.

Bantu. (1) — (6) are 30 boys and 30 girls from each of 3 schools, Tleseng (no bilharzia), Tweedepoort (almost 100% bilharzia), and Kana (about 50% bilharzia), all in the Native Reserve region 10 - 15 miles north-west of Rustenburg. (7) and (8) are respectively 21 boys and 24 girls from a rural Bantu school, in very poor circumstances. (9), (10) and (11) are 35 boys each from schools in the Johannesburg area, viz. Shalom Manne (Higher Primary School, Dube), Ebomini (Higher Primary School, Edenvale), and Farm School, Witkoppen.

Subjects were weighed and measured. Urine was voided between 9 and 11 a.m., except on 2 occasions (Kana Bantu School), when accurate 4-hour collections were made between 8.15 a.m. and 12.15 p.m. Volumes were measured, tests made for albumin ('albustix') and sugar ('tes-tape' or 'clinistix'), and the specific gravity determined. In certain groups individual samples were chemically examined; otherwise equal aliquots from samples were combined to provide a representative pooled sample from each school group. Samples were preserved by the addition of concentrated hydrochloric acid at a dilution of 1 per 100.

WEIGHT, HEIGHT, AND URINE NITROGEN PARTITION IN DIFFERENT 14–17 YEAR-OLD POPULATION GROUPS

Population group	*Sex*	*No. of subjects*	*Weight* (lb.)*	*Height* (ins.)*	*% Urea nitrogen / Total nitrogen*	*Urea / Creatinine*
Whites	M	38	118	65·8	85·5	25·0
Indian:						
(1) (better-class Moslem)	M	43	120	65·4	85·2	22·2
(2) (better-class Hindu)	M	41	112	63·6	84·0	21·5
(3) (poor urban Hindu)	M	45	96	62·0	73·2	13·7
(4) (poor rural Hindu)	M	30	90	62·3	72·4	12·8
Bantu:						
(1) (no bilharzia)	M	30	83	59·8	78·8	18·2
(2) (no bilharzia)	F	30	93	59·8	78·4	17·7
(3) (100% bilharzia)	M	30	82	59·3	76·3	16·8
(4) (100% bilharzia)	F	30	89	60·2	77·7	17·1
(5) (50% bilharzia)	M	30	80	59·4	78·6	17·2
(6) (50% bilharzia)	F	30	89	59·7	77·4	17·4
Bantu:						
(7) (poor rural school)	M	21	75	59·1	68·1	13·2
(8) (poor rural school)	F	24	78	58·8	66·2	12·0
Bantu:						
(9) Johannesburg area, Higher Primary Schools	M	35	99	62·3	81·6	20·1
(10) Johannesburg area, Higher Primary Schools	M	35	97	61·5	80·5	19·7
(11) Johannesburg area, Higher Primary Schools	M	35	102	62·4	82·1	20·8

* Weight and height data refer to the 15-year age group only in each school studied.

Total nitrogen (Kjeldahl method) was determined, and creatinine as described by King and Wooton.[32] Urea was estimated by the method of Levine *et al.*[33]

COMMENTS ON RESULTS

At Kana Bantu School, the two consecutive daily 4-hour urine collections for boys examined *individually* gave mean

nitrogen indices of 78·0% and 79·3%, and 16·9 and 17·6, respectively. The values for the first day's *pooled* sample were 78·6% and 17·1 respectively. Since agreement was close, only *pooled* urine samples from the other schools were examined for nitrogen, urea and creatinine.

Whites. The partition percentage, 85·5%, is closely similar to mean figures reported for White children elsewhere,[29,30,31] ranging from 82 to 91%. The urea/creatinine ratio, 25·0, corresponds with other reported mean values of 25·2 and 28·0.[30] Weights and heights are similar to those of Cape Town boys.[34]

Indians. The mean figures for the urines of the boys in the better-class schools (1) and (2), like their mean weights and heights, are similar to those of the White children. Values for the poorer Indian groups (3) and (4) are lower. In India, respective urine indices of 72·5% and 13·9, and 65·4% and 7·5 were found in adult groups of better-class (protein intake, 50·4 G.) and poorer (protein intake, 42·6 G.) Rajasthanis.[35]

Bantu. The values for the 3 Rustenburg male and female Bantu groups (1) — (6) are closely similar; hence these groups would seem to have similar nitrogen intakes. This inference is in harmony with the close similarity in mean age-group values for weight, height and skinfold, and for blood biochemical components (determined previously[6,14,15]). The mean figures are lower than those of the Whites or better-class Indians studied.

The other rural Bantu groups (7) and (8), who were unquestionably poor, had still lower figures. Children were underweight and under-height cmpared with Bantu groups (1) - (6). The former, moreover, were heavily parasitized in contrast to (1) — (6), who suffered only lightly from helminthic infestation.

The figures for the 3 groups of Johannesburg Bantu boys are closely uniform; the subjects would appear to have a greater intake of nitrogen than the Rustenburg groups. The higher figures of the former are in agreement with their greater mean weights and heights, which are about a year behind those of the White boys.

At Surinam, in Dutch Guiana, the following figures for children have been given urea-N/total-N percentage and urea/creatinine ratio respectively: Bush Negroes, 53 and 7·5, 76 and 11·1; Javanese, 79 and 13·7, and 85 and 18·8; Amerindians, 80 and 17·8;[30] and Kapaukus primitives, 50 and 4·4.[31] Edozien and Phillips[36] have reported percentage values of 79·5 and 54·9% for better-class and for poorer (low protein) Nigerian children, respectively.

While detailed figures are not given here, we found that albuminuria became progressively less frequent with increase in the two nitrogen indices. Incidentally, in the Bantu groups studied, the highest proportion showing albuminuria was 31%, which is a great deal lower than that reported for a Central African child group with bilharzia, namely, 73%.[37]

DISCUSSION

Do the partition percentages, combined with weight and height data, afford any information of value in relation to the specific problems mentioned? Before seeking to answer this question, it may be asked how representative are the samples studied? Of the White and Indian groups, all children normally go to school. This also applies to urban Bantu. But among rural Bantu, backward parents may restrict their children's attendance, especially during certain seasons; such groups therefore may not be representative. At the times of investigation, absenteeism in any group was not more than 5%; since we are dealing with pooled samples of urine, it is unlikely that the absentees would have made a significant difference to the results obtained. Within the limitations indicated, it is believed that the figures obtained are representative.

Turning now to the data acquired, it seems reasonable to suggest, on the basis of the information on the groups of boys, that the girls in the White and the two better-class Indian schools studied are comparable in nutritional state. Thus, if differences are found in mean times of onset of menarche, they are likely to be due to non-nutritional causes. If menarche is delayed in the girls in the poor Indian and in the Bantu schools, then inadequacy of nutrition may share responsibility. At the time of writing, menarche data are incomplete for certain of the school groups.

With regard to the Rustenburg Bantu children, only small differences in urine-nitrogen data were found between school-child groups with and without bilharzia *(S. haematobium).* These observations are in agreement with those on weight, height, clinical state, blood biochemistry and haematology, physiological tests (e.g. Harvard Step Test), and prowess in school-work studies, already undertaken on the three groups. The present findings narrow down still further the differences detected between the groups studied with and without bilharzia.[6,14,15]

The groups of boys in the diversely situated Johannesburg schools appear to have a similar nitrogen status. While a measure of undernutrition may well have been present, the existence of large-scale malnutrition is ruled out. A weakness in the study of pooled samples of urine is that data on a few well-nourished subjects may balance data on a few very malnourished subjects. In this connection, in each of the 3 Johannesburg schools a careful examination of 120 - 150 boys (undertaken for another purpose by Dr. S. D. Mistry) revealed much the same clinical picture: stigmata of severe deficiency were absent, and the only common lesion was follicular hyperkeratosis.

In the present study, interest has been focused primarily on the *mean* values of the various parameters determined. But, clearly, in the specific research problems previously detailed, determination of components in individual subjects presents no difficulty. Nevertheless, it is considered that the present approach probably holds out more promise for groups of subjects than for individuals, in throwing light broadly upon the nutritional state prevailing.

There is, however, an aspect of this type of investigation which is disquieting, and that is the legitimacy of comparing the various parameters in the non-White groups with those of the Whites, and assuming that when values in the former are lower than those in the latter, then in a measure undernutrition or malnutrition is implied. Too rapid growth in children may not be essentially meritorious; in the adult, at least, underweight is surely to be preferred to overweight. A high protein intake, consistent with a high urine urea/creatinine ratio, and with maximal muscle mass, need not be the optimum for the

organism. Certainly in respect of biochemical components such as serum cholesterol and blood sugar, the less privileged may have the advantage over the privileged. It is therefore of importance that care be taken not to draw too hard-and-fast conclusions (except in the presence of obvious deficiency) when making interracial comparisons.

SUMMARY

The need for knowledge of the general nutritional state of South African population groups has been emphasized, whether for public-health purposes, for determining changes in biochemistry and metabolism associated with elevation of socio-economic status, or for current research problems. A number of such problems have been instanced, and attempts have been made to learn whether, in so far as school children are concerned, the simple and easily determined parameters of weight, height, urea nitrogen/total nitrogen percentage, and urea/creatinine ratio, in pooled urine samples from large groups, can provide information of value. Observations suggest that this simple approach is promising and should be further explored and developed.

Gratitude is expressed to the school principals and teachers of the different schools for facilitating the examination of the children. For assistance in the field studies and laboratory work valuable help has been given by Misses A. Nurse, G. Schoen and P. Coles.

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CORRESPONDENCE

PARASITES IN STOOLS OF PERI-URBAN BANTU LIVING AROUND JOHANNESBURG

A NOTE ON THE INCIDENCE

To the Editor: A number of stools of obvious Bantu origin have been collected systematically from the veld within an annular belt 10–20 miles around Johannesburg. The stools were required primarily for the determination of their fat, iron and other contents, in connexion with investigations published elsewhere; but it was thought worthwhile to examine the faeces for the presence of parasites, to learn whether the incidence of the latter is likely to constitute a nutritional handicap to the inhabitants in the area investigated.

The number of stools collected was 158. The hypertonic saline flotation method was employed.

INCIDENCE OF HELMINTHIC INFESTATION

Parasite	*Number Infested*	*Percentage Infested*
Ascaris lumbricoides (Round worm)	34*	21.5%
Taenia sp. (Tape worm)	21	13.3%
Trichuris trichiura (Whip worm)	2	1.3%

*Ascaris infestation was mild in 23 out of the 34 positive stools.

Ancylostoma (hookworm) and *Schistosoma mansoni* (bilharzia ova) were not observed.

The only other published study upon parasitic infestation in non-Europeans residing in or near Johannesburg, is that of Porter (1918); of 375 male Coloured and Bantu patients admitted to the General Hospital, she found Ascaris to be present in 0.6%, and Taenia, 10.9%; other parasites amounted to 1.2%. The Ascaris infestation found by us is thus much higher than that occurring in Porter's investigation, although the Taenia infestation noted by her is slightly lower than our figure.

Ascaris infestations reaching 50% have been reported from Natal (Osburn, 1936; de Meillon and Holland, 1939; Elsdon-Dew, 1946; Gitlin and Schaffer, 1948). The same authorities have reported infestations of Trichuris to be common in Natal, 20.6–43% of the subjects examined being affected. In regard to Taenia, also in Natal, de Meillon and Holland (1939) reported an incidence of 14%, but Elsdon-Dew (1946) and Gitlin and Schaffer (1948) found only 2–3% infested.

It must be remarked that the present state of knowledge of the incidence of parasites among the Bantu in South Africa is far from comprehensive; while quite a number of studies have been undertaken on Native groups in Natal, and on Mine boys on the Witwatersrand, there is relatively little information available from the Orange Free state or from the Cape Province.

Should the findings in our brief investigation provide a correct reflection of the degree of parasitic infestation in the peri-urban Bantu around Johannesburg, it would seem that such infestation can hardly be regarded as a serious threat to the nutritional condition of these people.

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A. R. P. Walker, M.Sc. (Bristol), Ph.D. (Cape Town),
Ulla B. Arvidsson, B.Sc. (Cape Town),
W. L. Draper, B.Sc. (Tech.) (Manchester).

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Long term investigation of blood loss and egg load in urinary schistosomiasis in the adult African Bantu

BY

T. GERRITSEN, D.PHIL.

A. R. P. WALKER, M.SC., PH.D.

Nutrition Unit : Council for Scientific and Industrial Research, South African Institute for Medical Research, Johannesburg

B. DE MEILLON, D.SC., PH.D.

South African Institute for Medical Research, Johannesburg, and Bilharzia Natural History Unit: Council for Scientific and Industrial Research

AND

R. M. YEO, M.B., CH.B., M.R.C.S., L.R.C.P.

Medical Officer, Witwatersrand Native Labour Association Hospital, Johannesburg

LONG TERM INVESTIGATION OF BLOOD LOSS AND EGG LOAD IN URINARY SCHISTOSOMIASIS IN THE ADULT AFRICAN BANTU

BY

T. GERRITSEN, D.PHIL.*

A. R. P. WALKER, M.SC., Ph.D.

Nutrition Unit: Council for Scientific and Industrial Research, South African Institute for Medical Research, Johannesburg

B. DE MEILLON, D.SC., Ph.D.

South African Institute for Medical Research, Johannesburg, and Bilharzia Natural History Unit: Council for Scientific and Industrial Research

AND

R. M. YEO, M.B., CH.B., M.R.C.S., L.R.C.P.

Medical Officer, Witwatersrand Native Labour Association Hospital, Johannesburg

The investigation to be described forms part of a programme of research on the role of parasitic infestation in aggravating malnutrition in the Bantu.

Widespread infestation by *Schistosoma haematobium* occurs in several regions of the African continent (GELFAND, 1950a); in Natal, for example, CAWSTON (1918) reported an incidence as high as 80 per cent. among school boys in certain areas. While much information is available on the epidemiology, clinical picture, and pathology of the infestation, very little is known of the extent of the accompanying blood loss. Some authorities place this haematuria in the same category as blood loss in ancylostomiasis, and blood destruction in malaria, in its capacity to produce hypochromic anaemia (ERSPAMER, 1934; AWNY, 1944; BEET, 1945; GELFAND, 1950b; BROCK and AUTRET, 1952). Others suggest that schistosomiasis can cause a moderate anaemia (SALAH, 1935), or can merely aggravate an anaemia due to ancylostomiasis or malaria (ALLEN, 1936). TROWELL (1939) considers that the haematuria in urinary schistosomiasis is unimportant in so far as hypochromic anaemia is concerned. The position, however, must remain uncertain until quantitative information on the chronic blood loss is available, and whether such loss is likely to exceed the rate of the body's blood production, particularly when malnutrition is present.

Although the present investigation is concerned primarily with the blood loss, other relevant aspects, about which there is much uncertainty, have also been studied. For example, several authorities have drawn attention to the irregularity of the number of eggs discharged in the urine, and warn against making a negative diagnosis based on the absence of eggs in single sample (ORPEN, 1917; BLACKIE, 1932; CAMPBELL-BEGG, 1942; BENNIE, 1949). BARLOW (1948), however, refers to " the constant number of eggs which appear

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daily in the urine." Apart from incomplete data given by BARLOW and MELENEY (1949), no total egg counts undertaken over several days have been published.

The Witwatersrand Native Labour Association Headquarters in Johannesburg is the clearing station through which pass all in-coming Natives recruited for service on the gold mines. At the hospital attached to the above centre, where all Natives are examined, there were selected eight adult subjects (from Portugese East Africa, Angola, and Nyasaland), suffering from schistosomiasis with obvious persistent haematuria. Cystoscopic examination, kindly undertaken by Dr. G. C. THOMSON,* revealed that all subjects, save Fernando, showed bladder lesions of the most severe type seen at the hospital during observations extending over several years. Granulomatous masses, varying only in extent and distribution, characterized these cases; subject Fernando showed numerous patches of acne (bilharzial tubercles).

METHODS

Six subjects, outwardly in good health, were observed for 10 days, and two similar subjects for 19 days.

Collection of urines.

Urines were collected continuously over 12-hour periods, from 6 a.m. to 6 p.m., and from 6 p.m. to 6 a.m.

Determination of the blood in the urine.

This was carried out by determining the total iron content of the urine. A 100 ml. sample was dried in a silica dish over a small flame or on a hot plate, and ashed overnight in a furnace at dull red heat. After hot digestion with 5 ml. concentrated hydrochloric acid, 10 ml. water was added, and the extract filtered into a 50 ml. volumetric flask; further washings with small amounts of water were added, and the solution made up to the mark. To 25 ml. of the extract were added 10 drops of 90 per cent. thioglycollic acid and 5 ml. 7 N ammonia; the intensity of the purple colour was measured in a Hilger-Spekker Electrophotometer, using a 4 ml. cell and filter 603 (blue-green). Knowing the concentration of iron in the urine, and the total volume produced, the amount of iron excreted during each 12-hour period could be calculated.

Urine normally contains only a very small amount of iron; in Bantu subjects, the amount has been found to vary from 0.1 to 0.7 mg. per diem (WALKER and ARVIDSSON, 1950). As it is impossible to carry out separate determinations of metabolized iron, and of iron derived from haemorrhage into the bladder, it was decided to regard all the iron as originating from haemoglobin. The values given for the blood loss can be only slightly too high.

The amount of blood lost in the urine was calculated from the haemoglobin content of the subject's peripheral blood, and the amount of iron voided in the day's urine. Since haemoglobin = iron content x 34, then

$$\text{blood loss per diem in ml.} = \frac{\text{mg. iron loss per diem}}{\text{haemoglobin (g. per cent.)}} \times 34$$

Counting the eggs.

To estimate the total number of eggs in a 12-hour sample of urine, the total volume (minus the 100 ml. taken for determination of iron content) was poured into a separating funnel. After settling for a minimum of 2 hours, 50 ml. was drawn off into a centrifuge tube, and spun at 3000 r.p.m. for about 3 minutes. After decanting the supernatent liquor, the residue was suspended in a small volume (up to 2 ml.) of 0.9 per cent. sodium chloride solution, and well mixed. The total volume was measured

* Lister Building, Johannesburg.

in drops from an accurate 1 ml. pipette (1 ml. contained 19 drops), and the eggs present in four to six different drops were counted under the microscope. From these figures, the total number of eggs was calculated, correction being made for the 100 ml. taken off for the iron determination. Control tests showed that all eggs were accounted for by this method. The limits of error of the estimation were found to be within 10 per cent., which was considered to be adequate for the present purpose.

Blood.

Total and differential counts were carried out for all subjects.

For the determination of haemoglobin, the oxyhaemoglobin technique was used. 0.02 ml. blood was added to and shaken with 8.0 ml. of 0.1 per cent. ammonia, and the intensity of the colour, measured at 540 mμ, was compared with that of a solution of known haemoglobin content.

Faeces.

A sample of faeces from each subject was examined for *Schistosoma* ova (*S. mansoni* and *S. haematobium*), and for other parasites, such as *Ancylostoma* and *Ascaris*. For this purpose, the sodium sulphate—Triton centrifugalization method was used (FAUST, INGALLS and SEE, 1946).

RESULTS

The total number of eggs passed, the colour of the urine, and the amount of iron excreted, all per 12-hour periods, are tabulated in Table I.

The following data are given in Table II : cystoscopy grading; parasites in faeces and in blood; red cell count; eosinophils per c.mm. blood; haemoglobin in g. per cent.; total iron loss, total blood loss, and total eggs voided, during the 10-day periods of observation.

DISCUSSION

Colour of the urine.

The colour of the urine provided little guide as to the amount of blood lost. A urine of normal colour may contain slight amounts of blood; a brown or red urine may contain a very variable amount of blood.

Blood loss.

The average loss of blood per diem for the eight subjects observed, ranged from 1.3 to 6.1 ml. Our subjects suffered from the most severe schistosomiasis (in so far as cystoscopic appearance of the bladder was concerned) seen at the Witwatersrand Native Labour Association Hospital, through which pass about a quarter of a million African Natives per annum. The cystoscopist averred, however, that on extremely rare occasions, he had observed more extensive lesions of the bladder. It is possible, therefore, that the most severe infestations of schistosomiasis may give rise to a loss of blood greater than was observed in the present study.

Six of our subjects had haemoglobin values within normal limits—taken as 14 to 16 g. per cent. (WINTROBE, 1951). Although lower values were found with the two remaining subjects, both were infected with malaria, and one ,in addition, suffered from ancylostomiasis. Hence, our observations indicate that, except possibly in the most severe cases mentioned, the loss of blood in urinary schistosomiasis in adults is unlikely to cause hypochromic anaemia. As far as we are aware, no investigations have been undertaken to determine the maximum blood loss which can occur regularly without lowering the haemoglobin level in well nourished

TABLE I

Name:		Juao			Jim			Samendana			Kanivete			Fernando			Cuinhane			Litopote			Dominians		
Age in years:		27			23			19			26			19			24			22			30		
From:		Angola			Nyasaland			Portugese East Africa			Angola			Nyasaland			Portugese East Africa			Portugese East Africa			Angola		
Day		Colour of urine*	Number of ova passed in urine	Iron loss in mg.	Colour of urine*	Number of ova passed in urine	Iron loss in mg.	Colour of urine*	Number of ova passed in urine	Iron loss in mg.	Colour of urine*	Number of ova passed in urine	Iron loss in mg.	Colour of urine*	Number of ova passed in urine	Iron loss in mg.	Colour of urine*	Number of eggs passed in urine	Iron loss in mg.	Colour of urine*	Number of eggs passed in urine	Iron loss in mg.	Colour of urine*	Number of eggs passed in urine	Iron loss in mg.
1st,	d	B	25	0.38	D	85,000	1.75	B	350	0.62	—	—	—	D	50	0.98	C	13,200	1.32	D	11,950	2.39	D	16,800	1.00
	n	N	1,080	0.45	D	100	1.36	N	25	0.18	B	730	0.60	D	2,300	0.65	C	2,560	0.96	C	11,500		D	5,040	1.43
2nd,	d	N	830	0.29	C	73,000	1.77	C	3,500	0.78	N	1,600	0.64	D	40	0.70	B	14,200	0.84	C	26,000	1.12	C	900	0.54
	n	N	3,400	0.22	C	5,900	1.88	C	22,000	0.69	N	100	0.31	B	950	0.24	C	10,900	1.02	C	22,500		B	13,400	0.63
3rd,	d	B	840	1.08	C	17,800	1.59				N	280	0.59	N	60	0.09	A	1,390	0.52	C	40,500	1.88	C	230	0.83
	n	N	280	0.68	B	150	0.91	C	5,900	1.24	N	50	0.85	A	10	0.12	B	4,900	0.95				C	5,600	0.91
4th,	d	N	780	0.79	B	250	0.65	C	2,500	1.48	N	1,100	0.44	A	20	0.29	B	10	0.39	C	50,400	1.66	B	10	0.43
	n				B	850	0.82	B	880	0.52	N	150	0.38	A	680	0.12	B	2,850	0.82	C	450		B	850	0.38
5th,	d	B	250	0.36	A	7,600	0.48	C	8,200	0.98	N	240	1.40	N	450	0.11	A	5,750	0.28	B	4,900	0.87	B	18,900	0.64
	n	N	1,800	0.32	A	1,200	0.65	C	800	1.02	N			A	1,200	0.42	B	1,100	0.69	B	6,500		C	14,500	0.75
6th,	d	C	4,100	1.12	A	11,300	0.68	C	20,500	0.88	N	80	0.18	A	1,650	0.34	A	3,500	0.34	B	81,000	1.12	B	27,100	0.48
	n	N	520	0.61	A	43,000	0.73	C	21,200	1.48	N	25	0.45	N	1,250	0.20	A	1,800	0.63	B	34,500		B	12,400	0.76
7th,	d	A	3,100	0.45	B	59,000	0.89	C	640	1.25	N	220	0.59	N	1,900	0.17	C	17,800	0.44	C	67,000	1.46	C	17,800	0.93
	n	N	10	0.22	C	65,000	1.08	B	9,800	1.19	N	110	0.59	N	750	0.22	C	11,900	1.11	C	48,500		C	24,400	0.64
8th,	d	B	3,200	0.74	B	12,500	0.52	B	15,500	0.98	N	980	0.38	N	950	0.20	B	2,900	0.89	D	9,500	2.27	C	12,700	0.53
	n	N	5,900	0.28	B	950	0.62	B	25	1.11	N	810	0.09	N	1,000	0.18	A	100	0.68	B	24,000		B	19,800	0.32
9th,	d	B	7,800	0.49	A	1,500	1.15	C	900	1.44	N	40	0.11	N	650	0.37	B	17,500	0.61	C	800	1.72	B	9,800	0.48
	n	N	350	0.64	A	140	0.42	C	10	1.36	N	2,880	0.65	N	50	0.19	B	12,600	1.31	C	35,000		C	34,500	0.95
10th,	d	B	110	0.71	B	12,500	0.52	D	14,900	3.88	N	120	0.52	—	—	—	C	18,900	0.69	C	47,500	1.38	C	6,500	0.44
	n	N	280	0.38	B	9,500	0.59				N	1,800	0.57	N	180	0.10	C	4,250	0.66	C	18,500		B	16,300	0.24
11th,	d										N	1,900	0.64												

*Urine Colour Scale: N = normal; A = dark yellow, light orange; B = orange, light brown; C = red, brown; D = dark red, dark brown.

TABLE II

Name of subject	Juao	Jim	Samendana	Kanivete	Fernando	Cuinhane	Litopote	Dominians
Cystoscopy grading	+++	++++	+++	+++	+	+++	+++	+++
Parasites in faeces	ova *S. haem.*	ova *S. mansoni*	nil	nil	ova *S. mansoni*	nil	nil	ova of *Ascaris* and *Ancylostoma*
Parasites in blood	nil	malaria	nil	nil	nil	nil	nil	malaria
Red cell count (x 10^6)	6.38	3.76	5.19	5.98	5.20	5.60	5.33	5.85
Eosinophils per c.mm.	165	2,720	530	160	not done	not done	525	670
Haemoglobin g. per cent.	16.1	10.7	15.0	18.5	14.7	16.8	16.0	15.4
Total iron loss mg.	10.2	19.1	21.1	10.0	5.7	15.2	15.9	13.3
Total blood loss ml.	22	61	48	18	13	31	34	34
Total eggs passed	34,650	407,250	127,630	13,210	14,140	148,120	541,000	257,530

or in malnourished subjects. In acute haemorrhage in white subjects, as occurs for example in blood donors when losing 550 ml. blood, the haemoglobin level is restored to normal within an average period of 50 days (FOWLER and BARER, 1943). This suggests that a daily loss of 11 ml. blood may not cause hypochromic anaemia, but the inference is valid only if the haemopoietic response to haemorrhage is directly proportional to the amount of blood lost. To clarify the situation, a study has been initiated to determine the effect on the blood picture of the regular loss of small but increasing amounts of blood in both European and Bantu subjects.

Egg load.

For any one subject, the number of eggs present in consecutive 12-hour collections is liable to enormous variation. Thus, the subject Jim passed 85,000 eggs in the first 12-hour period; but during the 2nd, 6th, and 18th periods he was almost egg free. This finding emphasizes the warning given by previous workers (already mentioned) of the unreliability of seeking to diagnose schistosomiasis from single samples of urine.

Variation of egg load with time.

After completing our investigation, a peculiar regularity was noted in the number of eggs present in the urine, namely, that all subjects passed a minimum during the period from the 3rd to 5th days after the beginning of urine collections. This became apparent when the number of eggs passed, expressed as percentages of total eggs passed during the 10 days of examination, were plotted together in one graph (see Fig.). This minimum was

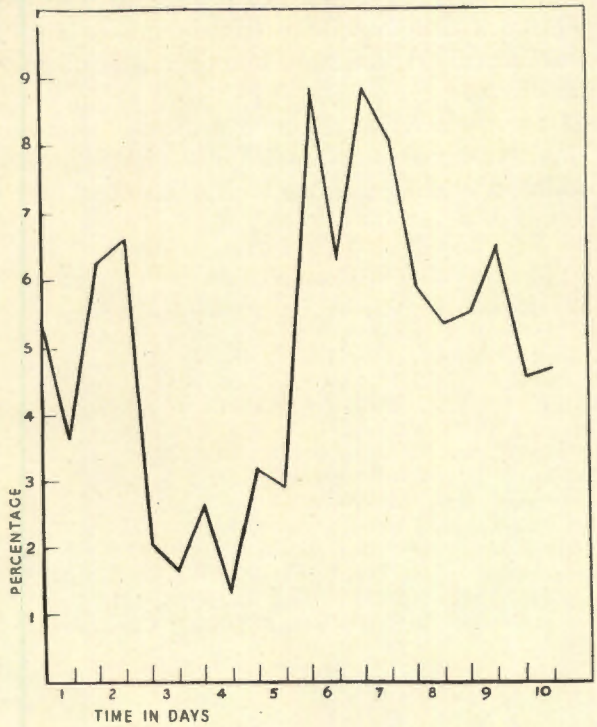

FIG.—Variation of egg load with time: egg load in percentage of total number passed during the period of 10 days.

followed immediately by a peak lasting for 2 or 3 days. That this finding is a coincidence is unlikely, and the following possible explanation is suggested. The collection of urine in all cases began between 1 and 3 days after the subjects reached Johannesburg, at the conclusion of a train journey lasting some days. On arrival, after the stress of this experience, haematuria was intense. The subsequent period of rest, during which time much lesser abdominal muscular activity occurred, would seem to have allowed the newly produced eggs to accumulate (BENNIE, 1949), and form vesiculae (BARLOW, 1948). Under pressure, these vesiculae rupture and discharge their eggs. This happened during the peak period on the 5th or 6th day. After this, the number of eggs passed (see Fig.) was less irregular, although the individual curves showed no regularity. In an endeavour to find out if this minimum and maximum would be repeated, the urine of two subjects was collected for a further 9 days; the same result, however, did not follow.

SUMMARY

Eight adult Bantu males from Southern Africa were selected, suffering from very severe urinary schistosomiasis (verified by cystoscopy) with persistent obvious haematuria. Urine was collected continuously in 12-hour periods, six subjects for 10 days, and two subjects for 19 days. The following are the salient findings :

(a) The colour of the urine is little guide to the amount of blood lost, and no guide to the number of eggs passed.

(b) The average amount of blood lost is smaller than was expected; it varied from 1.3 to 6.1 ml. per diem. The haemoglobin levels of six subjects lay within normal limits; lower values were obtained with the two remaining subjects, who, however, also suffered from malaria. It is concluded that in urinary schistosomiasis in adult Bantu males, the amount of blood lost is insufficient to cause hypochromic anaemia, but it might well aggravate an anaemia due to other causes.

(c) The number of eggs voided is subject to enormous fluctuation. One day there may be no eggs, and the next day tens of thousands. This irregularity once more draws attention to the unreliability of seeking to make a diagnosis of urinary schistosomiasis from single samples of urine.

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An investigation of haemoglobin concentration and of blood loss in stools in adult South African Bantu infested with intestinal *Schistosoma mansoni*

BY

A. R. P. WALKER,

DOROTHY C. FLETCHER

AND

VIVIEN TRAILL

Human Biochemistry Unit and Bilharzia Natural History Unit of the South African Institute for Medical Research, Johannesburg, and South African Council for Scientific and Industrial Research.

AN INVESTIGATION OF HAEMOGLOBIN CONCENTRATION AND OF BLOOD LOSS IN STOOLS IN ADULT SOUTH AFRICAN BANTU INFESTED WITH INTESTINAL *SCHISTOSOMA MANSONI*

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Human Biochemistry Unit and Bilharzia Natural History Unit of the South African Institute for Medical Research, Johannesburg, and South African Council for Scientific and Industrial Research.

Previous studies at this centre have included investigations on haemoglobin concentration, blood loss, and worm load, in urinary bilharzia (GERRITSEN, WALKER, DE MEILLON and YEO, 1952), and in hookworm infestation (GERRITSEN, HEINZ and STAFFORD, 1954). Before commencing a corresponding study on persons infested solely with intestinal bilharzia (*S. mansoni*), account was taken firstly of the lack of reports that the infestation causes an anaemia, and secondly of the prima facia evidence (mentioned below) which indicated the unlikelihood of arriving at any clear cut conclusions were such an investigation undertaken. Nevertheless, it was thought worth while to acquire the relevant information despite its limitations, since it falls within our wider programme of studying the aggravational effect of parasitism on malnutrition in the African Bantu.

In South Africa, regions infested with *S. haematobium* exclusively are known (PITCHFORD, 1952, 1954). On the other hand, according to present information, there appear to be no " pure " areas of *S. mansoni* infestation. The first requirement then, in order to carry out a satisfactory study, namely, the ready availability of persons infested solely with *S. mansoni*, cannot be met. Uncertainties, moreover, are increased by the probable presence of other helminths, by diseases such as malaria, and by other factors, both dietary and non-dietary, likely to affect haemoglobin level. Accordingly, we decided that we would merely divide the subjects to be studied into two groups, those with and those without demonstrable *S. mansoni* ova in stools. If the two groups showed no significant difference in haemoglobin concentration and the levels were satisfactory, then it could be inferred that *S. mansoni*, under the particular dietary and parasitic conditions prevailing, does not cause an anaemia. On the other hand, if observations revealed a significent difference between the two groups, a precise incrimination of *S. mansoni* would not be possible.

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With the above limitations in mind, in the first instance we studied (1) haemoglobin levels, the presence of blood in stools, and the presence of *S. mansoni* ova in stools, of medically fit Bantu mine workers coming from a region where both forms of bilharzia are known to be very common ; and (2) haemoglobin levels in Bantu farm labourers, values being determined in an area where the Bantu population are known to be approximately 100 per cent. infested with both types of bilharzia.

SUBJECTS AND METHODS.

Subjects.

(1) *Bantu mine workers.* The Witwatersrand Native Labour Association Headquarters in Johannesburg is the clearing station through which pass all incoming Natives recruited for service on the gold mines. At the hospital attached to the above centre, where all Natives are examined immediately upon arrival, we obtained blood, stools and urine from 96 Shangaans, coming from the Portugese East Africa—Transvaal border, a region where bilharziasis is common (PITCHFORD, 1952, 1954). All samples were taken from 9.30 to 11.0 a.m. Subjects were medically fit, and showed no obvious enlargement of liver, spleen, or lymph nodes. Ages ranged from 18 - 40 years.

(2) *Bantu farm labourers.* At Kaapmuiden, in the valley of the Crocodile River in Eastern Transvaal, infestation with both types of bilharzia is almost invariable (PITCHFORD, 1954). Blood was taken from 43 men and 40 women, collections being made mainly from 6 - 8 a.m. No detailed clinical information was available. Subjects, who were also Shangaans, were considered to be representative of their type. Ages ranged from 22-55 years.

Methods.

Haemoglobin was determined on venous blood by the oxyhaemoglobin method. 0.02 ml. blood was added to and shaken with 8 ml. of 0.1 per cent. ammonia, and the intensity of the colour measured using a Hilger Spekker spectrophotometer at 540 μ (Ilford Filter No. 602), calibrated against total iron determinations in blood.

Blood in stools. To determine the presence of blood in a stool, a portion of homogenized faeces about the size of a pea was placed in a boiling tube (20-25 ml. capacity) and an emulsion made with water (about 10 ml. water). The mixture was boiled to destroy any enzymes which would give a false positive result, and then cooled ; 2-3 ml. were acidified with 33 per cent. glacial acetic acid. An equal layer of 5 per cent. pyramidone was superimposed ; 2-3 drops of 30 volumes hydrogen peroxide were then added, allowing each drop to fall well into the solution. A lilac or mauve ring indicated the presence of blood. The test is less sensitive than the benzidine test, but equally as sensitive as the spectroscopic test. It can detect 1 part blood in 1000 parts faeces.

S. mansoni *in stools.* About 5 g. stool, mixed with 100 ml. aqueous 0.5 per cent. glycerin, was poured into a urine glass and allowed to settle for ½ hour. The sediment was washed twice further, settling for 20 and 10 minutes respectively. The sediment fluid was poured into a Petri dish and examined at 100 X.

S. haematobium *in urine.* Urine samples were settled and centrifuged, and a portion of the deposit examined for ova at 70 X.

RESULTS

Our results, firstly on the Bantu mine workers, and secondly on the Bantu farm labourers, are given in Tables I and II respectively.

Mean haemoglobin values have been calculated to sea level using Fitzgerald's Law (LURIE, 1945), namely, that there is a rise in haemoglobin level of approximately 10 per cent. per 100 mm. fall in mercury barometric pressure ; i.e. there is an approximate elevation of 2.4 per cent. per 1000 ft. rise above sea level. The mean altitude of the Shangaans' homeland is about 1000 ft. above sea level. While we have employed this correction factor,

we must point out that as far as we are aware, no relevant comprehensive long-term study has been undertaken on groups of persons rising from sea level to 5,000 - 6,000 ft., or vice versa. Normal values for white men and women are quoted after WINTROBE (1951).

TABLE I. Haemoglobin levels, and blood loss in stools, in Bantu adult males with and without *S. mansoni* infestation.

	Bantu group with *S. mansoni* present	Bantu group with *S. mansoni* absent
No. of subjects	24	72
Haemoglobin level g.% (mean S.D., and range)	15.2 ± 1.56 (12.9 — 17.9)	15.2 ± 1.35 (11.8— 17.7)
Mean haemoglobin level corrected to sea level g.%	14.6	14.6
No. of subjects showing blood in stools	6	16

Normal haemoglobin level of white men at sea level is 16 ± 2 g. per cent. (WINTROBE, 1951).

Additional data.

Three subjects who were infested solely with *S. mansoni* had haemoglobin concentrations of 17.7., 16.5., and 17.9., g. per cent. respectively.

Ova of *S. haematobium* were found in the urine of two subjects with *S. mansoni* ova in stools, and in the urine of two subjects without *S. mansoni* present. Ova of *S. haematobium* were also found in the stools of two subjects who had no *S. mansoni* present. Erythrocytes were present in 22 urines, including those which contained *S. haematobium* ova. It will be appreciated that the true incidence of *S. haematobium* is likely to be considerably higher than is indicated by the figures given.

Parasites, other than *S. mansoni* and *S. haematobium*, which occurred indiscriminately in the stools of the subjects of both groups included *Fasciola hepatica*, *Ancylostoma*, *Trichuris trichiura*, *Ascaris*, *Strongyloides*, and *Taenia saginata*.

TABLE II. Haemoglobin levels in Bantu farm labourers infested with both types of bilharzia.

	Bantu men	Bantu women
No. of subjects	43	40
Haemoglobin level g.% (mean, S.D., and range)	15.3 ± 1.5 (12.9 — 17.9)	13.3 ± 1.5 (10.6 — 15.8)
Mean haemoglobin level corrected to sea level g.%	14.7	12.8

Normal haemoglobin levels of white adults at sea level are 16 ± 2, and 14 ± 2 g.% for men and women respectively (WINTROBE, 1951).

COMMENTS ON RESULTS

Haemoglobin levels. The determinations on the mine workers were carried out in Johannesburg, the altitude of which is about 4500 ft. higher than the subjects' homeland.

Since blood samples were taken immediately upon arrival, we doubt whether there was sufficient time for any significant increase to have occurred in haemoglobin concentration. Data in Table I reveal no difference between the two groups of mine workers with and without *S. mansoni*. Levels of haemoglobin in each group, when calculated to sea level, are within the normal limits quoted for overseas healthy men. Data in Table II likewise, after correction for altitude, compare favourably with the overseas values cited for healthy adult males and females. These levels prevail despite the presence of several other parasites occurring indiscriminately, certainly with the mine workers, and probably also among the farm labourers.

S. mansoni *in stools*. According to FAIRLEY (1951), in mild infestations the presence of *S. mansoni* ova in stools is difficult to detect. Moreover, irregularity in the voiding of ova is well known. Diagnoses based on rectal biopsies are, of course, to be preferred (PITCHFORD, 1954), but to obtain such in our subjects was impracticable. The true figure for *S. mansoni* ova in stools is undoubtedly higher than the figure reported.

Blood loss in stools. The presence of blood in the stools of persons infested with *S. mansoni* is very rarely noticed visually. In positive cases, PITCHFORD (1954) considers the incidence to be about 1 per cent. It must be pointed out, however, that a haemorrhage consisting of specks of blood in a medium such as faeces is most unlikely to strike the eye. Our results show that 24 per cent. of Bantu with *S. mansoni* ova in stools, and 20 per cent. of those without *S. mansoni* ova in stools, showed blood in the faeces Unfortunately, the interpretation of the figures is limited by a number of uncertainties. Firstly, as already noted, difficulty of diagnosis in mild cases, and the irregularity of ova of *S. mansoni* appearing in stools, mean that the true percentage of positives is certainly higher than that recorded. Next, in a certain proportion of Bantu showing blood loss in their stools, the positive results could have been due to the haemoglobin present in incompletely digested meat residues. To carry out the test for blood loss satisfactorily, subjects should have lived on a meat free diet for 2-3 days. This course was quite impossible for us to arrange; in addition, it was out of the question for us to detain subjects for this purpose. Nevertheless, since the mine workers were examined immediately upon arrival, and since they had been travelling for 2 days or so, it is probable that in the majority of Natives, the intestinal tract was free from meat residues at the time of examination. The possibility that in some cases the blood loss may have arisen from peptic ulcer, carcinoma of the gastro-intestinal tract, haemorrhoids, etc., cannot be ruled out, although the rarity of these conditions among the Bantu (GELFAND, 1948) suggests that this possibility may be neglected. The actual amount of blood lost cannot be stated with certainty; but at the most it is unlikely to have exceeded a few ml. per diem. The uncertainties detailed do not, however, vitiate our conclusion, namely, that blood loss in infestation with *S. mansoni* is both irregular and small.

DISCUSSION.

Only in one complication of *S. mansoni* infestation, namely hepatic bilharzia, is anaemia reported to be common (ERFAN, 1947; FAIRLEY, 1951). For this condition, it is probable that hepato-splenomegaly is largely responsible. BLACKIE (1936) wrote of bilharzia being characterized by insidious blood loss, but as far as we are aware, no one has postulated that *S. mansoni* infestation *per se* can evoke an anaemia in man. Yet, were the reverse to be the case, whether from blood loss or other cause, it is very unlikely that an anaemia would develop in the South African Bantu on account of their excessively high iron intake, which is as much

as 200 mg. per diem (WALKER and ARVIDSSON, 1953). There is now ample evidence, recently presented and discussed by one of us (WALKER, 1954), that the habitually high iron intake of these people acts as a " brake " on the fall in haemoglobin levels which usually follows adverse dietetic and parasitic conditions. For example, even grossly malnourished pellagrins, as a group, do not show the anaemia which would normally be a feature of their condition (GELFAND 1948 ; KEYS, BROZEK, HENSCHAL, MICKELSEN and TAYLOR, 1950 ; NAPIER, 1952). This situation, however, also applies in measure to short-term consumers of a high iron intake. Thus, the restoration of haemoglobin levels in hookworm subjects by iron medication only, without improving diet, and without worming, has been demonstrated repeatedly (LAPAGE 1937 ; HYNES, ISHAQ and VERMA, 1946 ; CRUZ and PIMENTO DE MELLO, 1948). The same treatment has proved correspondingly satisfactory in malnourished hypochromic anaemic Chinese blood donors (SNAPPER, LIU, CHUNG and YU, 1939).

Our results, as expected, do not throw any light on the effect, if any, of infestation solely with *S. mansoni*, on haemoglobin levels. But they do indicate that such blood loss as does occur is infrequent and insignificant. We do not, of course, consider that *S. mansoni* infestation imposes no handicap on the good health of the host, but believe that in so far as the parasite does aggravate malnutrition and poor health, the blood loss constitutes no strain on haemopoiesis, and provides no avenue of loss of nutrients or metabolites.

SUMMARY.

(1) An investigation has revealed there to be no significant difference in mean haemoglobin concentrations in medically fit Bantu mine workers with and without *S. mansoni* infestation (but with other helminths present indiscriminately in both groups). Mean values, also those of Bantu men and women farm labourers in indifferent health and dwelling where infestation of both forms of bilharzia is almost invariable, have been found to lie within normal limits for healthy white men and women, after correction for altitude.

(2) Observations demonstrate that such blood loss as occurs with *S. mansoni* infestation is irregular and small, thereby providing neither a handicap to haemopoiesis nor an avenue of loss of nutrients or metabolites.

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Estimation of Blood Loss in Hookworm Infestation with Fe^{59}: Preliminary Report[1]

Th. Gerritsen, H. J. Heinz, and G. H. Stafford[2]

South African Institute for Medical Research, Johannesburg, and Council for Scientific and Industrial Research, Pretoria

A number of workers (*1, 2, 3*) have expressed the belief that in cases of hookworm infestation the anemia frequently observed could be caused solely by the blood lost from the intestines. In a review of the subject Lane (*4*) concludes that blood loss is the most probable reason for hookworm anemia. Wells (*2*) attached *A. caninum* to the intestinal mucosa of living dogs and from iron balance observations calculated the maximum loss of 0.8 ml blood per worm per day, but he allowed for a considerable variation in the blood consumption of individual worms. Hahn and Offutt (*5*) found a method of studying the blood loss in hookworm infestation of dogs using radioactive iron.

We have used a similar technic on three human patients, who, except for the hookworm ova found in their stools, were otherwise healthy. Our purpose was to determine whether the blood loss per worm per day was constant (improbable) and to what degree the blood loss was responsible for the comparatively low hemoglobin values of our patients.

Our method was briefly as follows. Approximately 40 μc of Fe^{59}, in acid solution containing less than 1 mg of iron, were sterilized, buffered, mixed with 20 ml of the patients' own heparinized plasma, and injected intravenously. Small samples of blood were taken at intervals of 2 or 3 days and the radioactive content measured. After about 8 days, this became approximately constant and the collection of stools was then started and continued for about 12 days. The stools were collected in periods of 3 days and lumped together for extraction of the iron and measurement of the activity. Finally, after the last 3-day period, the patient was dewormed and quantitative worm counts made on the stools for the next 5 days. Where possible, ova concentration methods were employed after the fifth day to check the efficiency of deworming.

The radioactivity of the blood was determined with an end-window Geiger counter after the sample had been ashed and electroplated on to copper disks, following essentially the method described by Vosburgh, Flexner, and Cowie (*6*). The stools were dried with concentrated HNO_3 on a water bath, ashed, extracted with HCl, and the activity of the liquid measured with a Veall type (*7*) liquid counter. A reference solution of Fe^{59} was also made from each batch used for intravenous injection. Then if

Cs = counts/min in the liquid counter of the stool ash extract,

Cb = average counts/min ml blood over the period during which the stools were collected,

Se = counts/min ml of the reference solution electroplated,

Sf = counts/min in the liquid counter of some of the same reference solution,

Vs = volume of stool ash extract in ml,

the blood loss is given by

$$(Cs \times Se \times Vs)/(Cb \times Sf).$$

Our results, as summarized in Table 1, appear to support Wells' conception of a considerable variation in the blood loss per worm. The daily loss of 10–20 ml (i.e., 5–10 mg iron) would seem to account for the hemoglobin values obtained. They are definitely low for Angola Africans, who have a high iron intake (*8*). The observed hookworm loads combined with a normal iron intake should, therefore, produce a marked anemia.

We feel for the present unable to explain the high blood loss of patient A, harboring such a small worm load, unless there are one or two profusely bleeding injuries left by the worms. To what degree blood loss is due to these bleeding injuries, or to the consumption of blood by the worm, remains to be determined in future experiments.

TABLE 1. Hemoglobin values; blood loss during subsequent 3-day periods; average blood loss per day; number of worms recovered from the stools after deworming; and blood loss per worm per day for the 3 patients examined, and one control.

Patient	Hb (g %)	Blood loss (ml)					Hookworms	Blood loss per worm per day (ml)
		1st period	2nd period	3rd period	4th period	Av/day		
M	10.7	33.5	26.8	25.1	28.7	9.5	368	0.026
A	13.1	48.6	30.8	47.9	—	14.1	63	.22
C	13.1	71.2	60.0	42.8	51.6	18.8	354	.053
Control	—	2.3	2.3	2.0	—	0.7	—	—

On the basis of our results, it is not necessary to argue that the anemia is caused by the effect of toxins (*9*). However, our results have been obtained on patients with light loads in the age group from 18 to 30 yr, and various factors such as adaptation and immunity might counteract the full effect of hookworm toxins and so affect our conclusions. There is, therefore, a need for further studies on younger patients and those with heavier hookworm loads.

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Studies on Parasitism and the Nutritional State *

by A. R. P. WALKER, *Human Biochemistry Research Unit, Council for Scientific and Industrial Research, South African Institute for Medical Research, Johannesburg*

The subject of parasitism and the nutritional state is one of considerable significance to non-white populations, particularly those dwelling in the tropics and semi-tropics, yet it has attracted relatively little serious attention. Consequently, the field is pervaded with speculation and differences of opinion.

For some time past, I have been collaborating with several other workers at the South African Institute for Medical Research in studies

* These studies were carried out in collaboration with the Bilharzia Natural History Unit (Hon. Director Dr B. de Meillon) of the South African Council for Scientific and Industrial Research.

on the blood loss that occurs in certain parasitic infestations. In particular, we have been interested in the claims frequently made regarding the role of certain parasites in causing or exacerbating hypochromic anaemia. Some of these studies are summarized below.

Blood loss in ankylostomiasis. By the use of radio-iron, we have found that the blood loss in hook-worm infestation is irregular (up to 18 ml a day in 3 young Bantu males), that it is not dependent exclusively on the number of worms present, and that it is certainly in harmony with the common and often severe hypochromic anaemia observed in regions where the parasite is common.[a] It is probable that the blood loss is greater in subjects with excessively heavy worm loads.

Blood loss in infestations with *Schistosoma haematobium*. An investigation on six young Bantu adult males suffering from severe urinary bilharziasis (diagnosed, *inter alia*, by cystoscopic examination) revealed a maximum average blood loss of 7 ml a day over 10 consecutive days.[b] A similar study (unpublished) on six hospitalized Bantu schoolchildren, likewise suffering from haematuria, revealed a slightly smaller daily blood loss. Notable features of both these studies were the wide variations in daily blood loss and the small amount of blood required to impart a marked colour to the urine. The haematuria found was unlikely to have caused an anaemia, but may have aggravated an existing one.

Blood loss in infestations with *Schistosoma mansoni*. Examination of the stools of patients with this infestation showed the loss of blood to be very small.[c]

Hypochromic anaemia in persons with bilharziasis. Blood examinations (haemoglobin concentration, haematocrit, and mean corpuscular haemoglobin concentration) in several groups of Bantu children and adults with both types of bilharziasis showed the number of cases of anaemia to be negligible. This finding, based on extensive field observations, is at variance with conclusions reached elsewhere. In Mozambique,[d] for example, anaemia is reported to be common, and occasionally severe, among bilharziasis sufferers. Nevertheless, it has not been established that bilharziasis is the causative factor, since anaemia appeared to be equally common among subjects with and without bilharziasis. Moreover, malaria is also prevalent and may share responsibility for the anaemia. It should be stressed that, in so far as our local studies are concerned, the rarity of anaemia may well be accounted for by the excessively high iron intake of the South African Bantu, which often reaches and occasionally exceeds 200 mg a day. In other regions, where the iron intake is moderate or low, it is possible that bilharziasis may cause a dyshaemopoiesis indirectly (i.e., quite apart from the haematuria) and hence promote an anaemia.

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[c] Walker, A. R. P., Fletcher, D. C. & Traill, V. (1954) *Trans. roy. Soc. trop. Med. Hyg.*, **48**, 501
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Comparative study of Bantu children with and without bilharziasis. Groups of children from two neighbouring Bantu schools, near Rustenburg, having access to different water supplies—one infested with *S. haematobium* and the other not—are being compared with regard to diet, anthropometry, blood chemistry, haematology, and parasitology. A record is also being kept of the clinical findings, studies are being carried out on the eyes and teeth, and various physiological and intelligence tests given. Observations up to the present suggest that the differences between child populations with and without bilharziasis are small. The general impression, therefore, is that the handicap imposed by bilharziasis may well be less than is usually believed. The work is continuing.

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The Problem of Seeking to Assess the Handicap Imposed by Parasitism on Certain Aspects of Health

ALEXANDER R. P. WALKER

South African Institute for Medical Research, Johannesburg, Republic of South Africa

I. Introduction

The problem of endeavoring to assess the influence of parasitism on physique, nutritional state, and other aspects of the health picture, is a profound one, and has received much attention in recent years. There have been careful reviews on the subject, for example, those of Hunter (1953) bearing on "Nutrition and Host-Helminth Relationships," and Smith (1955) and Geiman (1957), on "Parasitism and Nutrition" and "Nutritional Effects of Parasitic Infections and Disease," respectively. There have been comprehensive addresses on the subject, such as that of Chandler (1957) on "Interrelationships between Nutrition and Infectious Disease in the Tropics," delivered at the 1956 annual meeting of the American Society of Tropical Medicine and Hygiene. There have, moreover, been detailed symposia on the subject, as for example, that held at the above meeting on "Helminthic Infections as the Cause of Disability and Disease" (1957); and in the previous year's meeting there was a symposium in

which the corresponding situation with schistosomiasis was discussed (1955).

To the reader of these and kindred publications it soon becomes apparent that precise knowledge on the subject is very incomplete. Furthermore, examination of current relevant contributions indicates that little additional headway has been made to rectify the defective state of information.

The question naturally arises—why is knowledge on the subject so unsatisfactory? The answer is that in the contexts in which parasitic disease is a serious public health problem, the variables in the situation are so numerous that a precise apportionment of blame is well nigh impossible. Thus, Smith (1955) maintains, "we know very little about the metabolism or nutritional requirements of parasites, and . . . it is often almost impossible, especially in human subjects, to separate nutrition from a mass of other environmental influences which may have a bearing on host-parasite balance." Chandler (1957) even more emphatically states, "It appears . . . that infectious disease and malnutrition are so inextricably interwoven with each other that any attempt to deal with them separately, or separately to appraise their effects on the welfare of people in the tropics is as futile as trying to separate the effects of heredity and environment." Apart from parasitic and other zymotic diseases, and nutrition, there are factors such as housing, hygiene, tribal customs, etc. to be taken into account. How then can any rational approach be made toward the teasing out of the respective causes and deleterious effects?

The writer is not a parasitologist, but a biochemist and nutritionist, engaged in trying to throw light on the ramifications of patterns of diet on patterns of health and ill health among the interracial groups (whites, "Coloreds," Asiatics, Bantu) of South Africa. In pursuance of investigational work, it has been inevitable to wonder to what extent zymotic diseases, particularly helminthiasis, bear responsibility for the adverse aspects of the Bantu health picture. With this background, in seeking to clarify the problem under discussion, it has been thought worthwhile to review briefly the following closely related aspects:

1. Some avenues of approach to the problem, indicating their inherent limitations.
2. Criteria upon which parasitism might be expected to have an impact, in particular, physique and malnutritional stigmata.

The subject under discussion is so extensive that some restriction of scope is inevitable. Accordingly, it must be made clear that in this

iew, the writer almost exclusively has helminthiasis in mind, particu-ly schistosomiasis, ancylostomiasis, and ascariasis, and the handicap at they impose on the Bantu of South Africa.

II. Avenues of Approach in Seeking to Assess the Handicap from Parasitism

Smith (1955) has indicated that parasites may affect the nutrition of e host in the following manner:

A. Appropriation of nutrients,
   (1) From the host's food;
   (2) From the host's tissues.
B. Impairment of appetite and hence of food intake.
C. Disturbance of intestinal function in the host, causing impairment of digestion or absorption.
D. Disturbance of metabolism in the host, causing impairment of utilization.
E. Establishment and maintenance of immunity or resistance in the host to the parasite, requiring diversion of nutrients from the normal metabolic channels.

o obtain helpful information, enquiry may be pursued along the lowing avenues:

A. Determination of the nutritional requirements of parasites by means of *in vitro* studies.
B. Determination of the handicap imposed by specific parasites on experimental animals on different planes of nutrition.
C. Determination of the handicap imposed by specific parasites (from voluntary or involuntary infection) in healthy well-fed humans, *not* habituated to the environmental factors in which the particular parasite is endemic.
D. Observations on the health picture of humans habituated to unfavorable environmental factors including multiple nutritional deficiencies, but with a single parasitic infection.
E. Observations on the health picture of humans habituated to unfavorable environmental factors including multiple nutritional deficiencies and multiple infections.

Certain aspects of these approaches will now be discussed. The factors parasitism and nutrition as far as possible will be considered simul-neously.

A. *In Vitro* Studies on Parasites

Attempts to estimate the nutritional needs of parasites from *in vitro* studies are fraught with difficulty. Smith (1955) has pointed out, "*In vitro* studies which might provide much information, have so far failed to do so. In fact, no helminth infesting a mammalian host has been successfully cultivated in an artificial medium."

B. Animal Experimental Studies

It would be imagined at first sight that experimental studies on animals would be very rewarding, for, as Smith (1955) has indicated, there should be little difficulty in providing adequate, otherwise comparable, parasite-free controls, and in eliminating or compensating for many environmental variables. Unfortunately, investigations of this type are beset by numerous limitations and uncertainties. Obviously, the light that can be shed by studies on animals is determined by the measure in which the infection and its severity, and the nutritional requirements and stigmata of deficiency and excess, resemble the respective responses in man. The extent of the resemblance, however, both parasitologically and nutritionally, depends very much on the species and also the strain, sex, and age of the animal used. But there are additional difficulties.

1. Difficulties in Infecting Small Animals

According to Craig and Faust (1945), it is apparently impossible to accomplish a mature infection of experimental animals with the human strain of *Ascaris lumbricoides*. Schistosomiasis occurs naturally in man, monkeys, and cattle, and can readily be induced in mice, but not in rats, rabbits, or guinea pigs (De Meillon, 1960). In the beginning, therefore, there is some restriction on the types of animals that can be infected with parasitic forms of relevance to man.

2. Differences in Stigmata of Infection

A further limitation is that the stigmata of specific parasites in animals and man are not identical. There are points of difference in ill effects (lesions, liver dysfunction) in monkeys and man infected with *Schistosoma bovis* (Bersohn and Lurie, 1953). Blood loss in dogs from *Ancylostoma duodenale* (Wells, 1931) is far greater per worm than that estimated to occur in man (Gerritsen *et al.*, 1953; Foy *et al.*, 1958).

3. Difficulties Regarding Extrapolation to Man of Findings in Nutritional Studies in Small Animals

Chandler (1953) has emphasized, "Diet exerts profound influence on the course of parasitic infections." To obtain information from animal

experimental studies of value to man, it is necessary to study the effect of planes of nutrition on the course and severity of the parasitic infection. A major difficulty, however, is the fact that there are numerous differences between animals and man regarding nutritional requirements and malnutritional stigmata. Human diets, satisfying orthodox recommendations for nutrient allowances, are not adequate for the well-being of rats or monkeys (Sporn and Elvehjem, 1948; Sporn *et al.*, 1948). According to Gyorgy (1958), "Human milk is not only not beneficial, but is harmful for all animals used in routine nutritional studies." In no animals do the requirements of total protein or of amino acids correspond entirely with those of man (Hundley, 1958). Rats have a requirement of fat (Alfin-Slater and Deuel, 1960); this has not been demonstrated unequivocally with humans. A low calcium intake in rats soon produces stigmata and, *inter alia*, affects fertility (Henry and Kon, 1955); with humans this does not appear to obtain. Conversely, an elevated concentration of dietary iron of the level which will produce abnormal absorption and deposition (siderosis) in humans (Brown *et al.*, 1958) does not cause the same phenomenon in rats (Hegsted *et al.*, 1949). Many other differences between the responses of animals and man can be enumerated. There is, of course, no desire to minimize the valuable help that experimental nutritional studies on animals have yielded in relation to human nutrition and metabolism; but it is inescapable that the utmost caution must be exercised in the extrapolation of the findings from experimental nutritional studies on animals to man.

The foregoing considerations, both parasitological and nutritional, indicate that there are gross limitations to what can be learned from experimental studies regarding the handicap of parasitism in humans.

C. Observations on Healthy Humans with a Single Parasitic Infection

An avenue of approach which at first sight seems promising is study of the course and outcome of a single specific infection, self or involuntarily induced, in healthy subjects consuming a diet satisfactory according to current accepted standards. Naturally, voluntarily induced infection is undertaken by very few enthusiasts. Half a century ago, Looss (1911) infected himself with hookworm. He noted, *inter alia*, an increase in ova when additions of milk and cheese were made to purely vegetarian diet. Yet his observations have not been confirmed. Subsequent investigations of a similar nature have indicated that intestinal helminths generally benefit from lack rather than from excess of protein in the host's diet. More recently, it will be remembered how Barlow (Barlow and Meleney, 1949)

infected himself with schistosomes (*S. haematobium*); yet while his experiences, clinically and in other respects, are of great value, they tell us little of the precise toll that the schistosome exacts from underprivileged population groups among whom this parasite is prevalent.

In human nutrition, even carefully controlled studies involving deficiency of a single component have their limitations. Severe deficiency of calories, as in the well-known Minnesota study (Keys *et al.*, 1950) did not yield the same ill-health picture as the effects of involuntarily consumed semi-starvation diets. Although Crandon (1940) was able to induce scurvy in himself from prolonged consumption of a diet virtually free from vitamin C, the deficiency disease in its classic form did not eventuate in a long-term study on wartime conscientious objectors, consuming a diet adequate except for vitamin C (Medical Research Council, 1948).

Thus, "vivisectional" studies of the type described, both parasitic and nutritional, while certainly valuable, are unlikely to provide us with the needed information.

D. Observations on Underprivileged Peoples with a Single Parasitic Infection

As will be readily appreciated, it will be of great value to make observations on peoples habituated to inferior diets and accustomed to other unfavorable environmental factors (e.g., poor housing), but who have a parasitic infection either wholly single or grossly predominating. Opportunities, however, for making such observations are very meager. In South Africa on the highveld there are some Bantu population groups among whom *Ascaris* is the only helminthic parasite; there are others among whom *Schistosoma haematobium* occurs in the virtual absence of both blood-borne and stool parasites. Nevertheless, extensive studies by the writer and collaborators (Walker, 1958; Walker *et al.*, 1960) on Bantu school children with only *S. haematobium* infections have yielded disappointing and, in certain respects, anomalous results. Briefly, in Western Transvaal, in the Rustenburg Native Reserve region, by good fortune there are two nearby areas (4 miles apart), one where river water is used, and almost all consumers have bilharzia; and the other, where the source of water is shallow wells; and the incidence of bilharzia is negligible. Comprehensive studies on school children from these two areas have been undertaken—clinical, biochemical, hematological, physiological, tests for motor fitness, scholastic ability, etc.—yet, on the basis of the criteria used, it has not been possible to differentiate which children (whether groups or individuals) have bilharzia. Indeed, a number of paradoxical findings have been encountered which add confusion to an

already confused picture. Thus, the more intelligent children were found to be those who were infected; moreover, the better performances of the Harvard Step Test (a test of physical endurance) were by the infected children. From these observations, it is tempting to conclude that the handicap imposed by bilharzia on the children studied was not of significance to the total health picture. It must be noted, however, that lack of obvious stigmata may be explicable on the lines that (a) the infection was mild, frank hematuria being encountered only in about 10% of subjects; (b) stigmata may become prominent only in the older age groups (these studies are about to be undertaken); or (c) the children were fairly well nourished, thereby, presumably, mitigating ill effects of the bilharzial infection.

Along this avenue of approach, and even in an almost ideal situation for research such as has been described, results of investigations may be negative and contribute little toward elucidation of the problem at issue.

E. Observations on Underprivileged Peoples Habituated to Multiple Nutritional Deficiencies and Multiple Parasitic Infections

The people in these categories constitute the bulk of the world's population; they are the people about whom information concerning the effect of parasites, in the presence of nutritional deficiencies, is most urgently required.

Two investigations that have been undertaken on such peoples will be given for illustration. Many years ago, Lane (1932) presented a mass of evidence on the effect of heavy infection with *Ancylostoma duodenale* and *Necator americanus* upon the weight, strength, stamina, and performance of his adult human subjects, and noted the growth retardation, both physical and mental, which such infections cause in children. He further recorded the weight gains and general improvements in physical well-being and performance that resulted from eradication or even substantial reduction of the hookworm load.

A more recent investigation is described by Smith (1955). "The survey of a West African village (McGregor and Smith, 1952) was a baseline survey undertaken as a preliminary to an attempt to eradicate the common parasitic diseases without interference with the dietary, agricultural, social, or economics of village life, the object being to achieve as accurate an assessment as possible of the part played by the multiplicity of parasites in producing the ill-health and subnutrition so prevalent in the area. In the year after the initial survey, vigorous control measures were di-

rected against malaria, filariasis, and trypanosomiasis. Ancylostomiasis could not be attacked at this stage. The village was resurveyed just a year later. It was found that the total malaria parasite load had been reduced by 50% or more in the age groups of childhood and up to 80% in adolescence. The total load of microfilariae had been reduced by over 90%, and all persons known to be carrying trypanosomes had been treated. Reexamination showed that a considerable change in health status had occurred. The mean heights and weights of the children in all age and sex groups below six years were consistently higher than in the previous year, the difference, taking all groups together, reaching a high order of significance (p = less than 0.001). Hemoglobin levels had risen throughout the population, the mean increase being 17%. There was also noted a substantially reduced incidence of many stigmata of nutritional ill-health. The individual physical signs which decreased in incidence significantly were: folliculosis and dyssebacia of the skin of the face, cheilosis and angular stomatitis, indentation, fissuring and discoloration of the tongue, changes in the papillae of the tongue, and xerosis and 'crackling' of the skin of the limbs. With the exception of the last two skin manifestations, all these signs are generally attributed to deficiency of some member or members of the vitamin B complex, particularly riboflavin, niacin, pyridoxine, and possibly pantothenic acid."

Other investigations of this type could be described. It is postulated that among populations of the above type, it should be possible, by judicious selection and by long-term incremental specific deparasitization campaigns and nutritional enrichment campaigns, to clarify or at least to throw much additional light on the handicap under consideration. Indeed, this approach, although long-term and costly, appears to offer most promise for the future.

Up to the present, the factors parasitism and nutrition have been discussed together. But before leaving this avenue of approach, it must be stressed that there are other factors which, on occasion, have a strong modifying influence on health; and which, in seeking to apportion blame for the adverse effects in a total health picture, must certainly be taken into account. The influence that factors such as water supply, hygiene, and housing may exert, are obvious. But factors less understood and appreciated, since they vary so much from region to region, are local practices and customs, ignorance of which can easily lead to faulty conclusions from the type of research investigations just described. Since this aspect has received relatively little attention, a few illustrative examples will now be given.

F. The Influence of Local Practices on Nutrition and the General Health Picture

1. *Babies*

The following examples indicate how prejudicial local practices may be in relation to infant health picture. In earlier days, according to Keen (1946), 30% of South African Swazi babies died during their first year, the majority succumbing during the first month. There were many possible causes of this, malaria, syphilis, bad hygiene, ignorance, etc., but Keen stated that the main cause was the terrible custom among the Swazi that a newborn baby was not put to the breast until the umbilical cord had fallen off. This takes about 5 days, and during that time the baby is fed on soft maize meal porridge, made into a very thin paste and just pushed into the baby's mouth. As a second example, many Zulu mothers believe that their colostrum is not healthy for the baby, so they treat their breasts by squeezing them and applying hot fomentations for 2–3 days, or even as late as 5–6 days, before putting the baby to the breast (Jali, 1950). During this period weak maize paps are given, with or without sugar, with understandable deleterious effects.

2. *Children*

The following study illustrates how influential a little-known tribal practice may be on the growth of each sex of school children.

Over the course of a year, Keen (1946) made observations on a group of Swazi school children (boys and girls) at boarding and day schools. "The boarding school group grew as expected, with slowing down during holiday period when they worked hard in the fields. However, although the day girls grew regularly, the day boys gained practically no weight during the term time, but made similar gain to those of boarder boys during the holiday period. . . . The tremendous difference between the day boys and girls required investigation. On referring the factors to the Principal, it was noted that the day girls brought food with them. Without exception the day girls had a satisfactory mid-day meal, while very few of the day boys had anything to eat at mid-day. This meant that the average day for a boy was as follows: Breakfast at home—a long walk to school, sometimes as much as 4–5 miles,—a long day at school,—and a further walk home before any food was available. The Principal stated that during the year the only failures in Junior Certificate were among the day boys, in fact he considered it almost impossible to get a day boy through Junior Certificate. The matter was put to a meeting of the teachers, and we were informed that the Swazi male is not allowed to carry food, and that this was the prerogative of the female. The Swazi boy

would rather go hungry all day than degrade himself by carrying food to school. Here therefore was a little known Swazi custom which obviously accounted for the tremendous difference between the boys and girls."

3. Girls and Pregnant and Lactating Women

There are numerous reports bearing on abstinence from valuable foods by girls, pregnant and lactating women, due to tribal customs. The young adolescent Zulu girl is forbidden to consume eggs, since it is believed that females (especially young adults) become excessively fond of men as a result of consumption of this foodstuff. Eggs, moreover, are believed to lead to barrenness. Among the Mashona of Southern Rhodesia, Jali (1950) refers to certain tribes where mothers go through all their pregnancies without milk, this foodstuff being taboo.

4. The Effects of Urbanization

The effects of urbanization are widespread in their ramifications. Certainly medical treatment and hospitalization facilities are far in advance of those in rural areas, and urban Bantu are becoming increasingly hospital conscious. On the other hand, tribal discipline is greatly weakened, and promiscuity and venereal disease, relatively rare in most country regions, increase markedly with urbanization, as does tuberculosis. Concerning nutrition, whole grain or high extraction cereals progressively give way to white bread and sugar, a pattern all too familiar to those acquainted with the impact of white civilization on backward peoples (white and non-white). The whole subject is an enormous one and has many ramifications on physique and other aspects of the health picture. A few examples of changes will be given. (a) It is usual for Bantu mothers to produce breast milk adequate in amount and satisfactory in composition (Walker *et al.*, 1954b). In urban areas, however, the practice is being replaced by use of proprietary products, prepared almost invariably in too dilute a manner (Walker *et al.*, 1955). Even in Central Africa, Watt (1959) states, "Unfortunately dried milk preparations, widely advertised by press and hoardings, are gaining an unwelcome foothold." Unless prepared correctly, such preparations cannot but favor the development of infant malnutrition or even semi-starvation. (b) In rural areas, Bantu infants wear the minimum of clothing, and hence are exposed to abundant radiation. In such regions, many able clinicians of long standing (Gelfand, 1947; Trowell *et al.*, 1954) have yet to see severe rickets. On the other hand, the crowded conditions in urban townships, together with over-clothing, favor rickets, which is very common and often severe (Feldman, 1950). A corresponding situation prevails in centers of

population elsewhere, in India, China, etc. (Walker, 1955), and until recent decades, western cities such as Glasgow (Findlay and Ferguson, 1918). (c) Smith (1955) stated that "Even differences in dress may substantially influence exposure to insect-borne parasitic diseases, and the habit of wearing shoes is of importance in assessing extent of exposure to hookworm infestion." (d) Elsdon-Dew (1954) has shown that the incidence of *Entamoeba histolytica* is equally common in both rural and urban Zulu; yet there is a far higher incidence of the invasive disease in the urban dwellers whose diet is believed to be inferior to that of the rural dwellers.

These few examples emphasize that whether we are seeking to elucidate the ill effects of parasitism, of unsatisfactory dietary habits, or of other noxious factors, singly or in combination, it is imperative to take into account the modification influence of local practices.

III. Health Criteria as Affected by Parasitism

The first part of this contribution has concerned avenues of approach in seeking to elucidate the handicap imposed by parasitism on state of health. But in traversing these avenues, the question immediately arises, what changes in what criteria are to be looked for? In particular, which aspects of physique, or which nutritional stigmata are likely to be most adversely affected by parasitism?

Hunter (1953) stated that in intestinal helminthiasis in both man and animals, loss of weight is almost universal if the infection is heavy enough. Smith (1955) has stressed that the most common effect is loss in weight in the adult host or failure in the development of the young. In the first place, therefore, it is proposed to consider physique in an attempt to determine which aspects are most susceptible to the ill effects of parasitism.

In the following sections, the population used for illustration primarily will be the South African Bantu. In this respect, it must be made clear that both nutritionally and parasitologically, these people, in general, are at an advantage compared with most other indigenous African population.

A. Certain Features of Bantu Physique

The term "physique" has been defined as "The physical or bodily structure, organization, and development; the characteristic appearance or physical powers (of an individual or race)"—a definition, it will be observed, which includes more than the aspects of weight and height.

It is now proposed to enquire into the impact of parasitism, directly or indirectly, on the following aspects of physique: birth weight and prematurity, growth of younger and older children, height at maturity; certain

milestones of development, namely, psychomotor development of infants, and onset of menses; physique and physical performance—children at play, prowess at work, and physical endurance (Harvard Step Test).

1. Growth

a. Birth Weight and Prematurity. In South Africa, Heyns and Hersch (1944) collected single pregnancy records of 2298 labors of Bantu from two urban hospitals; 105 were stated to be unequivocally premature. The mean birth weight of the 2193 babies was 6 lb 12.4 oz; 67–70% of babies weighed between 5¾–7¾ lb, and 17% weighed under 5½ lb. In another series, numbering 500, however, in which all mothers had antenatal assistance, mean birth weight was 7 lb 4 oz. As a comparison, among whites of the same period, a local series of 942 babies (excluding multiple births) had a mean birth weight of 7 lb 8 oz, 5% weighing under 5½ lb (Le Riche, 1938). There is no doubt that birth weight characteristically is lower in underprivileged compared with western populations. As far as local somewhat meager evidence indicates, there appears to be no obvious difference between the birth weight of babies born among heavily parasitized Shangaans of the coastal region and lightly parasitized populations in certain highveld rural regions. From the data given previously it will be appreciated that since a single factor such as antenatal services, with minimal alteration in nutrition or treatment of zymotic disease, can have a profound effect on birth weight, it would be imprudent, without adequate evidence, to ascribe a large measure of blame to the parasitic factor for the almost invariable lower birth weight in underprivileged population groups. It may be remarked, incidentally, that a somewhat analogous situation appears to prevail in crop cultivation; in the growing of maize in South Africa, for example, it has been demonstrated that by weeding only, without fertilizers, sprays, etc., the yield of grain can be doubled.

The much higher incidence of prematurity in infants in the tropics and semitropics is well known. In central and southern Africa, it is well recognized that children whose weight at birth by ordinary standards would cause them to be classed as premature are often sturdy and active and can be reared without the special care that has to be lavished on white children of the same weight (Geber and Dean, 1957). In Johannesburg, Kahn *et al.* (1954) found that the survival rate among 1000 premature babies (almost exclusively under 4½ lb) *without* the use of incubators, special feeding, etc. compared not unfavorably with that of overseas white premature infants cared for in the orthodox manner. The incidence of prematurity in regions where parasitic disease is very common, compared with that in Johannesburg, for example, where parasitic disease is not a

serious health problem, has not been investigated. However, very limited knowledge from various local sources suggests that incidence of prematurity, as with birth weight, is not markedly influenced by the severity of parasitic infection prevailing.

b. Growth of Very Young Children. Jelliffe and Dean (1959) have stated that "African children of poorer groups, living under both rural and town conditions, show the following quite abnormal growth, as judged by weight gain, in the early years of life: (i) *First six months of life*: excellent growth with sufficient protein and calories supplied by a good flow of uncontaminated breast milk, while the child is protected from many infections by antibodies from the mother during pregnancy. (ii) *Second six months of life*: fair growth, but breast milk no longer sufficient for child's needs of both protein and calories, and added food (if any) usually mainly starchy carbohydrates, with little protein. (iii) *Second and third years of life*: poor growth, or even no growth, or loss of weight for long periods, due to the low protein, mainly carbohydrate diets (starchy foods, sometimes small quantities of breast milk, a little added animal protein, such as cow's milk, meat or fish), and to the numerous infections that occur (including diarrhoea, malaria, chest infection). During this stage, protein calorie malnutrition may occur. The two most common clinical forms are kwashiorkor and nutritional marasmus." Although written from Kampala, Uganda, statements similar to the above have emanated from the Congo (Meyers, 1951), Rhodesia (Gelfand, 1947), and South Africa (Salber, 1957; Kahn and Freedman, 1959). In contrast to the above, among Bantu groups in a more favored economic situation—as in the study of the latter quoted workers on children of Bantu nurses, sisters, and health visitors (with presumably minimal parasitization)—growth data (both height and weight) during the period of the study (1–11 years) were found to tally with those of Iowa City standards of "superior American children" (Jackson and Kelly, 1945). The ramifications of parasitism on the growth of very young children will be discussed with those older children (school children) in the next section.

c. Growth of Bantu School Children. Speaking generally, the height and weight pictures of Bantu children (rural and urban) almost invariably are inferior to those of contemporary white children, both local and overseas. Broadly, data combined from several studies (National Nutrition Research Institute, 1959) suggest that current height of Bantu children is of the same order as that of children in the United States (Hastings, 1957) at the turn of the century, and of British children a generation later, cited in the Board of Education Study of Newman (1928). There are exceptions, of course; for example, in the investigation of Welbourn

(1949), it was reported that of the Kampala Bantu children examined at 8 years and among whom the incidences of malaria, upper respiratory infection, and hookworm were high, mean height was *greater* than that of local white children of the same age group and, incidentally, coming from very good homes. Speaking generally, Bantu data for weight at various ages are slightly inferior to those of American and British children in the studies just cited. In comparison with poorer white children, for example, those in Dundee and Glasgow in 1920 (Paton and Findley, 1926), mean weights of Bantu boys and girls at 13 years are superior.

Local observations indicate that the height and weight of Bantu children habituated to a fairly satisfactory diet and lightly parasitized by *Ascaris* (for example, Bantu groups in Southern Kalahari Desert) do not appear to be significantly greater than those of Bantu dwelling in the coastal regions, where bilharzia, hookworm, and other parasites are common. However, investigations of growth and extent of parasitization in children from different local regions have not been adequately pursued, nor the effect of de-worming campaigns. It must be reiterated that in most local regions, severity of parasitization does not reach that occurring in the tropics.

There is another aspect to consider. Almost invariably birth weight and growth data are low in underprivileged compared with privileged populations, probably due largely if not exclusively to adverse environmental factors. It would be unwise, however, to infer that the underprivileged are at a disadvantage per se as long as their growth data fall short of values common to white populations. Cathcart (1940), quoting an earlier authority, once asked, "Should we aim, as some enthusiasts would have us do, at feeding children in such a way as to produce the maximum growth and development of which each child is capable? If we succeed in this are we sure that we have benefited the child? Does maximum growth make for health and longevity? There is certainly some evidence that it does not . . . ." Carlson (1942) noted that of the first 800,000 U.S.A. selectees in 1941, the mean height was 67.5 inches, the same as for the 1917–1918 draftees; but the 1941 recruits averaged 8 lb heavier. During that intervening period some have feared that physique deteriorated (Cureton, 1943; Perrott, 1941). In that instance the question arises, was that extra gain in weight essentially beneficial? While the foregoing is likely to have a bearing only on the most fortunate groups among underprivileged populations, it must be borne in mind that under-height and under-weight are not absolutely symptomatic of ill health, nutritional deficiency, or parasitic infection.

d. Height and Weight at Maturity. Table I indicates the height of

Bantu mine workers of 18–40 years (the group on which we have most information) to be little inferior compared with corresponding whites of the same age group.

TABLE I

HEIGHT OF MALE POPULATION GROUPS AT MATURITY

Observer	Population group	Number examined	Height (in inches)
Turner (1910)	South African Bantu		
	East Coast Bantu	1,337	66.5
	Transvaal Basuto	521	66.0
	Cape Province Bantu	680	66.25
Walker (1954)	East Coast Bantu	1,100	66.35
	Transvaal Basuto	650	66.25
	Cape Province Bantu	720	66.1
Carlson (1942)	United States Army Recruits	800,000	67.5
Clements and Pickett (1952)	Scotsmen, National Service Recruits	1,303	66.82

Additionally, we have found smaller groups of rural Pedi and Tswana Bantu males, 20–40 years, to have mean heights of 65.5 and 66.25 inches, respectively.

Regarding Bantu women, data are very inadequate. Small groups (100 or so) of Pedi and Tswana Bantu women, 20–45 years, were found to have mean heights of 60.5 and 61.5 inches, respectively. The mean height of Dundee mothers in poor economic circumstances studied in 1920 was 60.94 inches (Paton and Findlay, 1926). In the investigation of Kahn and Freedman (1959) the mean height of the privileged group of Bantu mothers was 62.3 inches, which is closely similar to that of Canadian women, 20–40 years, namely, 62.7 inches, reported by Le Riche and Pett (1955). Within the limitations of the studies cited, neither Bantu men nor women appear to be markedly inferior in height to white subjects.

Turning now to the parasitic aspect—in reference to Table I, "East Coast Bantu" subjects from Moçambique carry a far higher parasitic load compared with Bantu from the highveld (Beuchat, 1952). The white male groups cited presumably carried minimal parasitic loads. Yet the average height of the various male groups given is of the same order. Whereas parasitism, if severe, undoubtedly modifies *rate of growth*, it is questioned whether parasitism militates against attainment of ultimate height at maturity. The foregoing implies that the latter criterion may not be used as an index of severity of parasitism. The implication, of

course, refers to population groups only, and not to the constituent individuals.

B. Certain Milestones of Development of Bantu

1. Psychomotor Development in Very Young Children

At Kampala, Uganda, Geber and Dean (1957) reported that *newborn* Bantu children are at a more advanced state of development, judged by the criteria used, compared with normal white children. Much of the activity corresponds to an age of 4–8 weeks. In further studies on the psychomotor development of older Bantu children, these workers found that up to the age of about 3 years, development is usually in advance of white standards, the degree of advance being greater in the youngest children. These findings are not unexpected, because observations on Bantu children in the first year of life have already shown that the accepted "milestones" of development—raising the head, standing, walking, and so on—are passed at an earlier age than in white children. Unpublished observations of the same character have been made on Bantu infants in Johannesburg. Inhabitants of Uganda are heavily parasitized, and in the latter region, lightly parasitized. It is questioned, therefore, whether parasitism in mothers, or in very young children, has a modifying influence on the psychomotor development of the latter.

2. Menarche

Kark (1943) studied 1938 Bantu schoolgirls from four different rural areas in South Africa in relation to whether or not menstruation had commenced. In all groups investigated, no girls had commenced menstruating before 13 years, when only one girl had started. At 15 years, 40.5% of the girls were having menses; at 16 the majority (80%) had started, while it was only at 19 years of age that all the girls were menstruating. Kark discussed certain possible factors influencing menarche age, namely, nutritional state, disease, and climate; she considered physique and health to be important influencing factors, noting that in the groups studied, the menarche occurred a year earlier in areas of improved compared with less satisfactory nutrition. The latter conclusion agrees with various data given by Mills (1937), who noted, *inter alia,* that in Norway between 1868 and 1935, the mean age of onset declined from 16.1 to 14.5 years, a change undoubtedly related to improved standards of health and physique. In a recent unpublished study on 1000 girls in a Johannesburg Bantu township, Oettle and Higginson obtained a mean figure of 14.8 years. A current figure for British girls is 13.5 years (Wilson and Sutherland, 1953). To throw further light on the possibilities

of using this criterion (time of onset of menses) as an index of nutritional state, Oettle had initiated large scale studies on Bantu schoolgirls in several regions. By judicious selection of population groups, it should certainly be possible to determine to what extent the onset of menses is inhibited in regions of similar food resources and consumption, but varying grossly in parasitic load.

C. Physique and Physical Performance

1. Children at Play

Bantu school children at play appear to be more active than their white counterparts. In Bechuanaland, Squires (1949) considers that the general picture of vitality varies from school to school, and broadly correlates with nutritional state. We have reached the same conclusion after observing Bantu school children in a number of regions. Observations of the type described, admittedly highly subjective and necessitating a single observer, may well be useful in assessment of status in health surveys. The criterion, however, may not be of value among groups of white children, since inhibition of spontaneous activity is believed to increase with increasing income. In a limited number of studies among school children in different regions, comparison of parasites in stools and urines of "loafers" with the most active of children revealed no consistent correlation between level of activity and parasite load.

2. Physical Prowess at Work

In tribal life, it is usual for females to do the harder work—cultivating, weeding, fetching of water and fuel, "stamping" or grinding of cereals, and other household tasks. Men are concerned primarily with hut building, overseeing of the cattle, ploughing, and sowing. Although Bantu males pursue a more active life than white males, the former are not characteristically hard workers. Nevertheless, under conditions where heavy manual work is required, as for example with Bantu mine workers, their capacity, even without training, appears to be in advance of that of similar white workers (Wyndham, 1960). No comparison has yet been made between the performance of Bantu workers from regions of heavy as against light parasitization.

3. Motor Fitness

(a) *School children*: Le Riche *et al.* (1953) carried out studies using the Harvard Step Test on Bantu boys at a local institution for young delinquents. They found 90% to be in the "good, excellent, or superior" classes in comparison with 30% noted in a corresponding study on

American private school boys. We have carried out further similar studies on rural Bantu children, reaching the same conclusion.

(b) *Bantu young men*: Working with Bantu mine workers, Morrison and Strydom (1957) found that the performance of mining recruits compared with white students entering the University of Illinois (Cureton, 1947) were closely similar. The following mean scores for Bantu and whites were obtained: "Chinning," 8.55 and 9.81; "Dipping," 7.79 and 10.67; running the mile, 7.17 and 7.11 minutes; and for "push-ups," 15.62 and 16.49, respectively.

(c) *Older subjects*: In an unpublished study, Dr. P. J. Kloppers and associated workers have investigated Harvard Step Test performance by Bantu and white prisoners (long-term) at Pretoria Gaol. Everyday activity in the racial groups differed little, yet the Bantu showed significant superiority in performance.

This racial superiority of physical performance on the part of the groups cited, together with the previously mentioned anomalous results of step test performance of Bantu children with and without bilharzia, reveal a confused situation which stands in urgent need of clarification. Determination of the physical performance of population groups on much the same nutritional plane, but with a diversity of parasitic loads, must essentially form an important part of any research project bearing on the influence of parasitism.

From the foregoing sections, it will have been apparent that whereas certain aspects of physique in the Bantu, like rate of growth, undoubtedly are affected by parasitism, there is far less certainty regarding other aspects, such as height at maturity. Careful investigation is surely needed, therefore, in regions differing in parasitism and nutrition to throw light on which aspects of physique are best indices of the adverse effects of parasitism.

IV. Nutritional Deficiency Stigmata

In enquiring into the production or exacerbation of nutritional deficiency stigmata by parasites, it is necessary to bear in mind that "except in the case of a few individual nutrients, the better the host's diet, the poorer is the state of the parasites. Conversely, again with a few exceptions, it is the host with the poor diet and in a low state of nutritional health who harbours the most prosperous parasites" (Smith, 1955). In other words, it is the backward populations in the world, subsisting on inferior diets, with all attendant variables, who are most likely to suffer from adverse effects of parasites.

In relation to the protein situation, the results of numerous nitrogen

balance investigations on farm and laboratory animals indicate that those infected with intestinal helminths derive less value from their dietary intake than those uninfected (Hunter, 1953). In humans, however, findings are not consistent. Thus, Venkatachalam and Patwardhan (1953) found that the excretion of nitrogen almost halved when Indian children with heavy loads of *Ascaris* were effectively dewormed. Bray (1953), however, did not confirm this observation when studying malnourished Gambian children with ancylostomiasis and ascariasis. Obviously, further investigations of this type are urgently required. Jelliffe (1953) believes that heavy ascariasis among infants may be a major contributory cause of nutritional deficiency syndromes of the kwashiorkor type in West African babies.

In respect to stigmata of vitamin deficiency, as far as one is aware, it has not been demonstrated that the course of rickets and osteomalacia, or of scurvy, is affected by the presence or absence of parasites, apart, of course, from changes in nutrient intakes consequent on impairment of appetite. Stigmata of deficiency of members of vitamin B complex have been shown to be aggravated by the presence of parasites—this having been demonstrated in the field studies of McGregor and Smith (1952) previously described. The macrocytic megaloblastic anemia due to the fish tape worm, *Diphyllobothrium latum*, arising from competition for vitamin B_{12} by both parasite and host, is well known.

As far as one is aware, the only mineral element of major importance to nutrition whose deficiency may be caused or aggravated by parasitism is iron. The slight blood loss considered to occur in ascariasis (Brown, 1934) is still a matter for conjecture. But in schistosomiasis, study of the hematuria in severe *S. haematobium* infection in a group of South African Bantu mine workers revealed a mean blood loss of about 7 ml per diem when observed over several days (Gerritsen *et al.*, 1953). In *S. mansoni* infection, marked blood loss appears to be uncommon (Walker *et al.*, 1954a). Hookworm infection, of course, can be responsible for considerable blood loss; an early study from this laboratory using radio-iron indicated a mean loss of about 10 ml blood per diem from 3 Bantu mine workers. Later studies by Foy *et al.* (1958) revealed mean blood losses of the order of 12 ml per diem occurring in heavy infections. These workers point out, however, that there are a number of anomalies in the situation; for example, there is a lack of correlation between incidence of hookworm and anemia in many of the surveys made in the past 20 years in different parts of the tropical world.

It will be readily apparent that among underprivileged populations, much further work remains to be undertaken before a clear picture can

emerge of the bearing of parasitism on the causation or aggravation of malnutritional stigmata.

V. Discussion

There can, of course, be no doubt about the magnitude and importance of the subject under discussion. According to Stoll (1947), throughout the world humans infected by worms exceed two billion; of that number, three parasites—ascaris, hookworm, and trichuris—account for almost three quarters of all helminthic infections (Stoll, 1957). Actual death rates from worm infection vary according to the region. De Silva *et al.* (1953) in Ceylon consider that *Ascaris* causes the highest fatality rate of any intestinal parasite, hookworm coming second. As a cause of death (although not of morbidity), schistosomiasis, as it occurs in the Union of South Africa, is not a problem (Elsdon-Dew, 1958).

It will have become abundantly apparent that the difficulties described by earlier writers as impeding assessment of the handicap imposed by parasitism on nutritional state, or on total health picture, have not been exaggerated. As will have been appreciated, and recently underlined by Platt (1958), the major drawback to elucidation is the fact that various noxious influencing factors, singly or in combination, may yield much the same ill health syndrome. Thus, malaise, coated tongue, hebetude, easy fatiguability, loss of power of concentration, and delayed reaction time of the special senses are among the many features attributable, in either the presence or absence of parasites, to chronic malnutrition; equally, these signs and symptoms are features of chronic constipation as it occurs in western populations (McLester and Darby, 1952). Not infrequently, ascariasis is accompanied by poor digestion of food and diarrhea, and at times an acute inflammation of the bowel; these phenomena may arise not only from other zymotic diseases, but from certain types of grossly unsatisfactory diet, at least among the very young. According to Smith (1955) "the microcytic, hypochromic anaemia of ancylostomiasis is primarily an iron deficiency anaemia. . . . It differs in no way from the anaemia produced by dietary iron depletion or repeated haemorrhage and can be largely cured, and rendered completely orthochromic, by the administration of additional iron without the removal of parasites." Many other examples illustrative of ambiguity of etiology could be cited.

In a subject like the present one, the caution urged long ago by Virchow (1847) is singularly apposite. "How then can one with certainty determine which of two consecutive phenomena is cause and which effect, and whether either is in fact cause and both not simultaneously effects of a third factor, or indeed, that each is not the effect of two quite distinct causes?"

What are the prospects of clarification that lie ahead? Undoubtedly, all avenues of approach will contribute information of value. But in the final instance, it is necessary to concentrate primarily on malnourished populations with their almost ubiquitous parasitic loads. As already indicated, real progress is likely to come primarily from long-term studies with adequate controls, in which the variables of the contexts are altered singly. It will be apparent that several representative regions will need to be studied, due to differences in basic nutritional backgrounds. Thus, the parasitic handicap in regions where cereals are the predominant source of energy is likely to be of less moment than among populations subsisting on less nourishing roots and tubers. The parasitic handicap from hookworm infection obviously will be more severe in Uganda, for example, compared to Zululand where the indigenous population are habituated to an excessively high iron intake (Walker and Arvidsson, 1953).

In a paper of the present character, it is all too easy unintentionally to simplify the problem under discussion. Most aspects have been dealt with briefly, indeed, superficially. The term parasitism has been restricted primarily to consideration of helminthiasis, which in turn has been limited chiefly to ascariasis, bilharziasis, and ancylostomiasis, as they occur and affect the Bantu of South Africa. It is hoped, however, that the avenues of approach described, and the physiological and other criteria considered as likely to be affected by parasites will be applicable to, or at least have a bearing on, situations throughout the world where parasitism is a serious public health problem.

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PART II : STUDIES BEARING ON CALCIUM METABOLISM IN BANTU CHILDREN AND ADULTS.

PART II. STUDIES BEARING ON CALCIUM INTAKE, METABOLISM AND DEFICIENCY IN THE BANTU.

1. INTRODUCTION.

Although enormous progress has been made in the science of nutrition during the present century, there is still considerable uncertainty over the minimum physiological requirements of many nutrients. This applies especially to calcium. South Africa is a very suitable country for investigating the effect of low calcium intakes, since there are two populations available for study, Bantu and White, who are habituated to low and high calcium intakes, respectively. There are, of course, other differences, dietary and non-dietary, between the two populations.

2. RECOMMENDED ALLOWANCES OF CALCIUM.

Until recently, dietary standards bodies in most countries recommended a calcium intake of 800 - 1000 mg. per diem for adults. In South Africa, in 1956, the relevant Committee (of which the writer was a member) concurred, while recognizing inadequacies in the available evidence.[24] The Expert Committee for "Calcium Requirements" (of which the writer was also a member) set up by F.A.O./W.H.O. (1961) considered that in the virtual absence of evidence to the contrary, recommended intakes for adults could be scaled down to 400 - 600 mg. per diem.[25] All standards committees have recognized that a large proportion of the world's population ingest less, often considerably less, than current recommended allowances of calcium.

3. DIET AND CALCIUM INTAKE OF THE BANTU.

The South African White population eats similarly to that in Britain, United States, and like countries. The diet includes plenteous calories, with high intakes of protein, fat, and calcium.

Speaking very generally, the diet of the Bantu[13] (excluding that of weaned infants and very young children) is probably adequate in calories and gross protein, low in animal protein and fat, and high in carbohydrate. It is low in calcium, but high in phosphorus, with an

milligrams of the element per diem. One research group has suggested that the inferior height of children in the tropics and semi-tropics may be due, in part, to this cause. In seeking to throw light on the problem, the writer investigated groups of Bantu children, consuming similar diets, although dwelling in hot and cooler regions. It was found that they grow at roughly similar rates.[30] Hence, the points raised, (i) and (ii), in so far as practical nutrition is concerned, may well be unimportant to the population group concerned.

The calcium situation in Bantu women is prejudiced, of course, by multiple pregnancies and long lactations.[27]

4. CALCIUM DEFICIENCY STIGMATA

The main difficulty confronting attempts to elucidate the deleterious effect of a low calcium intake is that the ill-effects of calcium deficiency have not been defined.[25] When a diet is very low in calories, or in certain single dietary components, such as protein, iron, iodine, and the vitamins, the stigmata resulting are predictable, and remediable broadly by treatment with the respective nutrients.[31] But this does not apply to calcium whose clinical and pathological stigmata are not known with certainty.[25]

In enquiring into the ill-effects of a low calcium intake it is considered that the best approach lies in studying the integrity of the various physiological processes in which the element is involved. Accordingly, during a period of many years, studies have been carried out in the following respects:- Rate of growth; calcium concentration of breast milk; composition of bone (ribs and vertebral bodies), arterial tissue and serum; the prevalences of rickets, osteomalacia, osteoporosis, and dental caries. These studies will now be mentioned briefly.

5. RATE OF GROWTH.

In inter-racial studies, quite apart from differences in calcium intake, there are so many other factors, dietary and non-dietary, which influence growth, that no firm conclusions on the role of calcium intake can be reached.[31a] The following points, however,

are deemed of importance:-

(i) Bantu babies when wholly breast fed for the first six months grow as rapidly, sometimes more rapidly, than White babies. In explanation, as already indicated, Bantu breast milk has much the same average composition as that from White mothers in respect of the major nutrients; moreover, most Bantu mothers lactate profusely.

(ii) While under-privileged children grow less rapidly than better-class children, whether White or Non-White, it is questioned whether slower growth in otherwise outwardly healthy children is necessarily deleterious.[14] We have found, as expected, a more rapid growth in Bantu children with rise in socio-economic level.[16] We have also found that good growth can take place in spite of an inferior diet (in the orthodox sense) and heavy parasitic loads.[15]

(iii) Adults in under-privileged communities usually are shorter than those in prosperous communities.[14] But again there appears to be no evidence either that the inferior height attained is due specifically to a lower intake of calcium,[31a] or that among otherwise healthy adults shorter stature is prejudicial to the enjoyment of good health and well-being.

6. CALCIUM CONCENTRATION IN TOTAL BODY AND IN BIOLOGICAL COMPONENTS.

(i) Percentage of calcium in total body.

We have no data on total body calcium in the Bantu. In balance observations carried out on under-privileged persons habituated to a low calcium intake, subjects usually are found to be approximately in balance. This situation is accomplished by means of a higher apparent percentage absorption, and a lower urinary excretion of calcium, compared with subjects accustomed to much higher intakes. We have obtained confirmatory evidence of this type from mineral salt balance studies on Bantu prisoners.[32] However, even when allowing for the usually smaller frames of low calcium underprivileged consumers, it is probable that they have a lower percentage of calcium

in their bodies. Arithmetically, it seems unlikely that the Bantu, from their meagre calcium intakes, have the same opportunity for accretions of bone compared with, say, the White subjects studied by Malm. Furthermore, in somewhat crude studies, in which comparison was made of bone density of arm and wrist of Bantu and White subjects on the same X-ray plate, we found that Bantu bones are thinner than those of Whites. Possibly, however, this phenomenon may have a genetic origin, since thinness was also noted in bones of better class Bantu.[14] Further and more detailed studies on this aspect are needed. Notwithstanding, it would seem that a lower concentration of total calcium in the body need not be deleterious: almost undoubtedly a lower concentration obtains with elderly Bantu mothers.

(ii) Composition of breast milk.

Investigations in Africa, India, and elsewhere, have shown that a low calcium intake does not necessarily lower the concentration of calcium in breast milk. As noted previously, we have found that milk from Bantu mothers has virtually the same calcium concentration as that from White mothers.[1,2]

(iii) Studies on bone.

(a) Composition of bones: ribs and vertebral bodies.

Our investigations (with Dr. J. Higginson) on ribs (5th) from Bantu and White subjects (infants, children, adults) revealed normal histology, and no significant differences in mineral salt composition (ash, calcium, phosphorus) of the dried, defatted (and occasionally de-marrowed) bones.[33,34] The observations made are in harmony with those of Nicholls and Nimalasuriya (1939) who found very little difference in the percentage of calcium in bones (tibia and femur) from Singalese and White subjects. The studies on vertebral bodies (5th. thoracic) from Bantu and White subjects revealed that in bodies from the former, there was slightly greater mineral matter per unit of both dry weight and volume, and more calcium per unit volume of bone ash.[35] In agreement with this observation, bones from U.S.A. Negroes have been found to be denser than those of Whites. The scope of our investigations on bone composition and density have not been exhaustive, but in the respects indicated it would seem that

low consumers of calcium are not at a disadvantage.

(b) Integrity of bone: Miscellaneous considerations.

There is no evidence, locally (or elsewhere so far as the writer is aware), that low calcium consumers have bones of inferior strength compared with high consumers. (1) In the Transvaal, our studies on school-children of different racial groups (Bantu, Indian and White) have not revealed significant differences in the prevalence and anatomical distribution of fractures of long bones.[32] (2) In the South African gold mines, where about a third of a million Bantu mine-labourers from different regions are employed, physicians of long standing aver that Bantu workers under physical stress are not more liable to fracture their limbs compared with Whites; moreover, physicians have the impression that for similar injuries, e.g. broken arm or leg, lesions in Bantu possibly heal more rapidly.[36] (3) A report from Central Africa indicates that African adults subjected to electro-convulsive therapy experience about half the frequency of fractures of limbs compared with White subjects; the explanation of this difference, however, is not known. (4) Examination of cross-sections of vertebral bodies reveal that, in general, the trabecular framework is more profuse, although thinner, in Bantu compared with Whites. Mechanical tests, in which the force required to crush vertebral bodies was measured, have yielded variable results, although, broadly, no difference was apparent between the findings on Bantu and White bones.

(c) Rickets and Osteomalacia.

It is often assumed that a low intake of calcium causes or promotes the occurrence of rickets; an examination of evidence, however, failed to substantiate this view.[37] In tropical and semi-tropical countries, and even in temperate regions, it would seem that, with certain exceptions, provided full advantage be taken of available radiation, rickets is not a problem.[8] Yet, when full advantage is not taken, rickets may be common and severe, even where sunlight is plentiful. Thus, rickets has been reported to occur in crowded urban centres in India, Nigeria, South Africa, and elsewhere.[8] Locally, in Johannesburg,

rickets is common, sometimes severely so, in Bantu children under two years; but among rural Bantu, despite an equally low intake of calcium, we have noted that rickets rarely is seen.[8] Regarding adult rickets or osteomalacia, it has been shown both in India and China, that the disease is closely associated with insufficient exposure to sunlight, rather than with a low calcium intake. Among the Bantu of Southern Africa, no case of osteomalacia appears to have been reported.[8,36,37]

(d) Osteoporosis

In Western countries, in a number of recent reports, it has been concluded that osteoporosis primarily affects low consumers of calcium, also subjects who absorb calcium poorly. In Southern Africa, osteoporosis among under-privileged peoples has been insufficiently studied. Nevertheless, ~~it is~~ the disease is scarcely, or not at all mentioned in text books of medicine on the African. In Johannesburg, in certain Bantu, generalised osteoporosis with collapse of vertebrae has been noted. But the disease occurs (1) almost exclusively in males; (2) chiefly in those under 60 years; (3) usually in association with siderosis, and (4) often in association with scurvy. Presumably, osteoporosis, as thus depicted, is a special environmental phenomenon. A detailed examination of the subject of osteoporosis and calcium deficiency suggests (1) that a low calcium intake per se does not cause or promote the development of osteoporosis; and (2) that a racial factor may well be involved.[27] Senile and post-menopausal osteoporosis should be ubiquitous in elderly Bantu, especially females; this does not appear to be the case.[27] Hence, osteoporosis, like so many other phenomena associated with ageing in western populations, ~~is not~~ cannot be regarded as being linked with the ageing process per se in man.[38]

(e) Dental Caries

The prevalence of dental caries among less privileged populations often is lower than among nutritionally more

favoured populations. Numerous studies have shown that the possession of sound teeth is consistent with a low calcium intake. In studies on groups of rural Bantu children, we have found that about 10 per cent have carious teeth; in urban Bantu, the proportion reaches 50 per cent or more;[16,32] in local Whites, the proportion has been stated to be about 90 per cent.

(iv) Calcium concentration in arterial tissue.

In elderly South African Bantu it has been shown that mean concentration of calcium in the aorta is much lower than that found in White subjects.[39] Furthermore, it has been found that in aorta from Bantu and Whites having equal pathological grading (naked eye assessment), the Bantu have a significantly lower calcium concentration.[39] The promotive rôle of excessive calcification of aorta and possibly of other arteries in relation to coronary heart disease has not been defined; but if reduced fat intake be recommended to reduce atheroma, then, logically, a lower calcium intake should be recommended likewise.[40]

(v) Serum calcium concentration : Tetany

In several studies, mean serum calcium level has been shown to be about 10 per cent lower in under-privileged compared with nutritionally more favoured populations.[36] We have suggested that this lower value is influenced primarily by the lower calcium intake, and that the phenomenon is not necessarily pathognomonic, no more so than lower serum cholesterol or blood sugar levels in such people. There appears to be no evidence, however, that the simple addition of calcium salts to primitive diets will raise serum calcium level to that of "normal" Whites, although the subject has not been intensively studied. To throw light on this aspect, we are determining serum calcium levels in Bantu population groups consuming similar diets but differing grossly in the calcium concentration of their drinking water. Among individuals in populations, whether White or Non-White, it is not known whether high or low serum calcium levels are associated with high or low intakes of the element. The

finding of relatively lower serum calcium values in the Bantu enjoins caution over the interpretation of laboratory data in population groups differing in race or environment.[41]

Tetany.

This condition is not rare in severely malnourished Bantu infants. The causative factors are not clear, and further investigation is needed to determine to what extent, if any, low calcium intake is responsible.

7. MISCELLANEOUS.

(i) Urinary calculi.

The occurrence of urinary calculi in Bantu is virtually unknown.[42] But such calculi are common among certain Indian populations who are also low consumers of the element. The rôle of level of intake of calcium in the aetiology of the condition has not been established.

(ii) Gall stones.

The prevalence of gall stones, and certainly of cholelithiasis, is far lower in Bantu compared with Whites.[40] Among populations consuming a pattern of diet resembling that of the Bantu, namely, European populations several generations ago, also certain war-time populations, cholelithiasis was relatively low or became reduced. The bearing of calcium intake or of serum calcium levels on the development of the condition is not known.

(iii) Blood coagulation.

Calcium plays an important rôle in blood coagulation. Exhaustive studies by Mersky et al, in Cape Town, however, failed to reveal significant differences in respect of several blood coagulation tests when comparing Bantu with White subjects.

8. SUMMARY.

Summarizing, - the information adduced on various physiological processes in which calcium, directly or indirectly, is involved, indicates that a low calcium intake is not necessarily prejudicial to the normal physiology and metabolism of the body.[43]

Trowell has stated that "until it can be demonstrated that the tissues of Africans suffer by reason of a low calcium content, it appears unwise to speak of deficiency." However, regarding White populations, knowledge is inadequate of the long-term effects of a low calcium intake in persons previously accustomed to a high intake, although war-time experience does not suggest that widespread unequivocal ill-effects are likely to ensue.

The problem of how the Bantu (and similarly placed populations) manage to use their meagre calcium intake to such, apparently, good effect, may be explained by the mechanism referred to, namely, by increased absorption and decreased urinary excretion, which together permit sufficient retention of the element to occur for normal physiological processes.

9. SUGGESTIONS FOR FURTHER RESEARCH.

(i) Endeavours must be made to intensify the carrying out of growth studies on population groups of similar nutritional status but habituated to the consumption of drinking water of widely different calcium concentration. This is certainly possible in South Africa.

(ii) Clarification is required on whether low consumers of calcium do indeed have a lower percentage of calcium per total body compared with high consumers. It would seem especially desirable to secure this information on under-privileged populations, especially mothers, whose diet and manner of life are beset by numerous known nutritional handicaps. The obtaining of such information, of course, will be difficult.

(iii) It is desirable to undertake further studies of bone density and composition in different populations, Bantu and White, and in groups of subjects from extremes of socio-economic levels, with special reference to children, pregnant and long-lactating women, and, especially elderly subjects.

(iv) It is needful to carry out long-term studies in different racial groups to determine ~~whether~~ the extent by which low consumers or poor absorbers of calcium are significantly more prone to develop osteoporosis compared

with nutritionally more favoured individuals. In the East and Far East, it is desirable to determine to what extent a low calcium intake influences the development of osteomalacia.

(v) Further study is required on the degree and significance of calcification of arteries, in particular, of aorta, coronary and cerebral vessels, in different population groups.

(vi) In ethnically "pure" populations, providing that great extremes of rich and poor are found, it would seem desirable to determine serum calcium levels, protein fractionation patterns, and levels of other biochemical components, to throw more light on the factors influencing or associated with low serum calcium levels. The population groups in mind would include prosperous Bantu traders and indigent Bantu peasants, poorer Indians in India and Indian immigrants to South Africa, also affluent South African Whites and "Poor Whites".

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NOTE: Reference 28. This contribution must be excluded from the assessment of papers for the degree, since the research work involved was used for the degree of Ph.D.Cape Town University.The paper is included simply to indicate the full scope of the research work undertaken in this section.

PART II.

STUDIES BEARING ON THE METABOLISM OF CALCIUM BY BANTU CHILDREN AND ADULTS.

COPIES OF PAPERS PUBLISHED OR IN PRESS

NATIONAL NUTRITION COUNCIL

RECOMMENDED MINIMUM DAILY DIETARY STANDARDS

COMPILED BY THE DIETARY STANDARDS COMMITTEE OF THE COUNCIL

1. In 1935, the League of Nations[1] made the first attempts to define man's daily requirements of specific nutrients in quantitative terms. The Committee on Foods and Nutrition of the United States National Research Council published a much more detailed table in 1941 which was adapted to South African conditions by the National Nutrition Council in the following year. The American figures were revised in 1945, 1948 and again in 1953. In 1953 the National Nutrition Council of South Africa decided to revise its own standards and in the present report the existing knowledge of the subject is applied to the somewhat unusual circumstances of a country with a mixed population that varies greatly in its dietary habits and occupations.

Existing Standards

2. The Dietary Standards of the Food and Nutrition Board of the National Research Council (NRC) of the USA are recommendations and not requirements 'since they represent, not merely minimal needs of average persons, but nutrient levels selected to cover individual variations in a substantial majority of the population. . . . The nutritive intakes recommended are, in general, higher than the average requirements and lower than the amounts which may be needed in pathologic states or in rehabilitation following depletion'.[2]

3. The figures given by the Committee on Nutrition of the British Medical Association, 1950[3] are intended to be adequate for the maintenance of a good nutritional standard for healthy persons. These standards also do not make provision for sickness or convalescence.

4. The standards of the Canadian Council on Nutrition (1950) are even lower than the British, and serve as a basis for determining food supplies of groups, and can also be used for judging the adequacy of the food intake of individuals, or groups. 'They also indicate a nutritional floor beneath which maintenance of health in people cannot be assumed'.[4]

5. In 1950 a Committee of the Food and Agriculture Organization FAO recommended methods that may be followed in assessing calorie requirements. Their recommendations are designed for application to countries or groups within countries. It is emphasized that the recommendations are not directly applicable to individuals and, even when applied to groups, local circumstances must be considered. The Committee considered requirements at the 'physiological level'; their recommendations represent the needs of healthy individuals and are 'set at such levels as to make possible an active life and a high degree of productivity in occupational pursuits'. They are based on a 'reference' man (weight 65 kg., 143 lb.) and woman (weight 55 kg., 121 lb.), aged 25 years living at a mean external annual temperature of 10°C (50 F). Suggestions are made for calculating the requirements of individuals differing from the 'reference' in respect of body size, age, activity and environmental temperature.[5]

General Principles

6. There is no evidence of racial differences in the requirements of nutrients; consequently no distinction between the standards proposed for Whites and non-Whites has been made in the table.

7. The nutrient requirements of individuals are influenced by sex, age, activity, ideal weight and other factors. If actual weight be taken as the basis, a corpulent person will gain weight owing to the higher calorie-allowance provided, whereas the needs of an underweight person will not be adequately met. If ideal weight for height, activity or body surface could be used as the criterion, the calorie requirements could be assessed more accurately; unfortunately adequate data for South Africa in this respect are lacking.

8. The close relationship or interaction of the different nutrients is a subject of much research. The intake of one nutrient probably affects the requirements of others. Thus the thiamin requirement is determined by the calorie content of the diet; both folacin and vitamin B_{12} play a part in the synthesis of choline, which is essential for the maintenance of liver morphology and function; vitamin D promotes the absorption and metabolism of calcium; a deficiency of niacin occurs particularly in diets low in complete proteins—such proteins provide the essential amino acid tryptophane, which is a niacin precursor.

Use and Limitation of Dietary Standards

9. It is most important to remember that dietary standards cannot be used as the only criterion for judging the nutritional state of a person or group, and that failure to comply with these standards will not necessarily lead to deficiency diseases.

10. In this connection the following quotations are of interest:

'Inasmuch as many persons who receive less than the recommended allowance of one or another nutrient may remain in health through long periods, it becomes apparent that these allowances are not to be used as the sole criterion for judging the state of nutrition of any population.'[6]

'If these allowances are used in dietary evaluation, it is essential to appreciate that, while most persons whose consumption equals or exceeds the goals are presumably adequately nourished, not all persons who fail to reach these goals are malnourished.'[2]

'It is important that standards should be correctly applied and their limitations recognized. In the past some of the conclusions drawn from the comparison of nutrition intake levels with the dietary standards have been far from valid. If the results of a dietary survey show that the diet has a very low calorie content, the conclusion that the group in question is suffering from undernutrition is perhaps a legitimate one. But the fact that the intake of certain nutrients falls below some recommended allowance does not justify the conclusion that a proportion of any group surveyed is suffering from malnutrition. In such circumstances the possible presence of malnutrition may be inferred, but the dietary survey *per se* provides no evidence of its existence.

The value of the information is that it indicates where further investigation may be needed and which dietary defects need most consideration in food and nutrition programmes.'[7]

Proposed Dietary Standards for South Africa

11. The standards proposed here should be regarded as adequate for the maintenance of health without allowing for a safety margin for ill-health, or for great individual differences in absorption and metabolism. The physical changes of the normal body with age and activity have been taken into consideration; for example, from the age of 10 years the requirements of boys and

girls are considered separately, because of differences in weight, activity and earlier changes in girls than in boys.

12. The figures given are for nutrients in foods as consumed and do not allow for losses during transport, storage, preparation or serving. Little is known regarding the extent of these losses. It is probable that little or no loss of protein or carbohydrate usually occurs but with certain methods of cooking, e.g. broiling and roasting much loss of fat may occur. Mineral salts, e.g. calcium, can be leached out of vegetables during cooking in water. The losses in vitamins may be very high, especially of ascorbic acid. Figures from the literature show the following average losses in vegetables during cooking, depending on the

TABLE I. RECOMMENDED MINIMUM DAILY DIETARY STANDARDS

	Calories (*a*)	*Protein* *g.*	*Calcium* *g.*	*Iron* *mg.*	*Vit. A* *I.U.*	*Thiamin* *mg.*	*Riboflavin* (*o*) *mg.*	*Niacin* (*q*) *mg.*	*Ascorbic Acid* *mg.*
Man (average weight 160 lb.)									
Moderately active	3,000	65	0·7	9	4,000 (*k*)	1·0	1·6	15	40
Sedentary Worker	2,300	65	0·7	9	4,000 (*k*)	0·8	1·6	12	40
Heavy Worker ..	4,500	65	0·7	9	4,000 (*k*)	1·6	1·6	18	40
Woman (average weight 130 lb.)									
Moderately active	2,300	55	0·6	12	4,000 (*k*)	0·8	1·4	12	40
Sedentary Worker	2,000	55	0·6	12	4,000 (*k*)	0·7	1·4	11	40
Heavy worker ..	2,800 (*b*)	55	0·6	12	4,000 (*k*)	1·0 (*b*)	1·4	15 (*b*)	40
Pregnancy, last trimester	(*c*)								
Moderately active	2,600	80 (*g*)	1·5	15	5,000 (*l*)	0·9	2·0	14	55
Sedentary worker	2,200	80 (*g*)	1·5	15	5,000 (*l*)	0·9	2·0	13	55
Heavy worker ..	3,200	80 (*g*)	1·5	15	5,000 (*l*)	1·1	2·0	15	55
Lactation	(*d*)	80 (*g*)	(*i*)	15	6,000 (*l*)	(*n*)	(*p*)	15	55
Children									
0–3 months ..	55 cal/lb.	1·6 g/lb. (*h*)	0·8 (*j*)	6 (*h*)	1,500 (*m*)	0·2	0·5 (*h*)	2 (*r*)	20 (*s*)
4–9 months ..	50 cal/lb.	1·6 g/lb. (*h*)	0·8 (*j*)	6 (*h*)	1,500 (*m*)	0·3	0·8 (*h*)	4	25 (*s*)
10–12 months ..	45 cal/lb. (*e*)	1·6 g/lb. (*h*)	0·8 (*j*)	6 (*h*)	1,500 (*m*)	0·35	0·9 (*h*)	4	4 (*s*)
1–3 years ..	1,100	40	0·6	7	2,000 (*l*)	0·4	1·0	6	40
4–6 years ..	1,500	45	0·7	8	2,500 (*l*)	0·5	1·1	8	40
7–10 years ..	1,900	55	0·8	10	3,000 (*l*)	0·7	1·4	10	40
Girls									
10–12 years ..	2,400 (*f*)	70	1·0	12	3,000 (*l*)	1·0	1·8	12	40
13–15 years ..	2,600	75	1·2	15	4,000 (*l*)	1·1	1·9	15	40
16–20 years ..	2,400 (*b*)	70	1·2	15	4,000 (*l*)	1·0 (*b*)	1·8	15 (*b*)	40
Boys									
10–12 years ..	2,400	65	0·8	12	3,000 (*l*)	1·0	1·6	12	40
13–15 years ..	3,000	75	1·3	15	4,000 (*l*)	1·2	1·9	15	40
16–20 years ..	3,700	90	1·3	15	4,000 (*l*)	1·5	2·3	15	40

(*a*) Although a single figure is given in each instance, it must be regarded as an average around which there is an individual range. In any case the calorie allowance must be adjusted to the needs of the individual so as to achieve and maintain his desirable weight (see Table II).
(*b*) In the case of female heavy workers, e.g. those working in the fields, this value may have to be appreciably increased.
(*c*) The basal metabolic rate of the mother is not altered by pregnancy and the increased metabolic requirements are due to the foetus and increased weight of the mother.
(*d*) Add 120 calories for each 100 ml. of milk produced, e.g. at 1 month the average milk production is about 700 ml. and allowance should be made for 840 calories. At 4 months production is about 1 litre and allowance should be made for 1,200 calories.
(*e*) For groups under 1 year allow approximately 1,000 calories.
(*f*) Allowance has been made for lesser activity compared with boys but this is balanced by greater need because puberty changes set in earlier.
(*g*) An additional allowance of 25 g. is made both for pregnancy and full lactation; half of the allowance should be derived from animal sources.
(*h*) The recommendation for infants pertain to protein, iron, etc. derived primarily from cow's milk or commercial milk-preparations.
(*i*) Add 120 mg. calcium for each 100 ml. of milk produced; e.g. at 4 months the allowance would be 1·2 g.
(*j*) Where breast milk is not being used.
(*k*) Assuming that 1/3rd is present as vitamin A, or 5,000 I.U. if 1/5th is present as vitamin A.
(*l*) Preferably 1/3rd in each case as vitamin A.
(*m*) There is evidence that the intake of vitamin A from breast milk, though highly variable, is approximately 2,000 I.U. at 2 months and 2,500 I.U. at 4 months, but it is not yet established that these intakes are necessary.
(*n*) Allow 0·4 mg. for each additional 1,000 calories—see (*d*).
(*o*) See paragraph 26.
(*p*) For full lactation the allowance should be 2·0 mg. riboflavin.
(*q*) See paragraph 27.
(*r*) This figure is based on the known concentration of niacin in breast milk and bearing in mind that pellagra amongst children reared entirely at the breast is unknown.
(*s*) Based on the vitamin C concentration in breast milk.

TABLE II. RELATIONSHIP BETWEEN CALORIE REQUIREMENTS AND DESIRABLE WEIGHT [5]

Weight lb.	Weights: Man Calories	Man Percentage of allowance for reference man	Woman Calories	Woman Percentage of allowance for reference woman
240 ..	4,035	135		
230 ..	3,912	130		
220 ..	3,787	126		
210 ..	3,660	122		
200 ..	3,532	118	3,151	137
190 ..	3,402	113	3,034	132
180 ..	3,271	109	2,918	127
170 ..	3,137	105	2,798	122
160 ..	**3,000**	**100**	2,677	116
150 ..	2,863	95	2,554	111
140 ..	2,723	91	2,423	105
130 ..	2,579	86	**2,300**	**100**
120 ..	2,433	81	2,170	94
110 ..	2,283	76	2,036	88
100 ..	2,125	71	1,900	83
90 ..	1,972	66	1,759	77
80 ..	1,809	60	1,614	70

Reference man: 160 lb. **Reference woman: 130 lb.**

method employed.[5] The low figure is for waterless cooking and the high one when the foodstuff is covered with water. Losses are due to leaching (riboflavin and niacin), actual destruction (ascorbic acid) or both (thiamin):

Carotene	5—21%
Thiamin	9—37%
Riboflavin	12—37%
Niacin	9—41%
Ascorbic Acid	27—47%

Ascorbic acid is progressively destroyed by an oxidizing enzyme liberated in many fruits and vegetables after they have been picked. It is thus most desirable that the interval between picking, preparing and serving these products be as short as possible.

13. The weight of the average South African man or woman is not known, but it has been decided to adopt the arbitrary figure for the reference man of 25 years of 150 lb. (73 kg.) and for the reference woman of the same age, of 130 lb. (59 kg.).

Adjustments of calorie requirements for weights other than those of the reference man and woman are given in Table II.

14. In the higher age-groups, especially when the occupation is sedentary, the calorie intake from both carbohydrate and fat sources can be reduced with advantage in order to prevent obesity and certain degenerative diseases, but the intake of other nutrients should not be reduced. On the contrary, because the body changes from the anabolic to the catabolic state, the nutrient intake other than carbohydrate and fat may well need to be increased rather than decreased.

15. As is well known the requirements during pregnancy and lactation are higher than those for non-pregnant and non-lactating women. In some instances (e.g. calories, protein, calcium) it is possible to calculate the additional needs from the known composition of the products of conception or of breast milk. In the case of many other nutrients, little is known of their requirements, though it is generally agreed that they should be increased.

Calories

16. Since external temperature affects calorie requirement, extreme variations must be taken into consideration. An average temperature of 60° F has been used in drawing up these standards, following the adjustments for external temperatures made by FAO.[5]

17. At 1 year the requirement is approximately 45 calories per lb. body weight (100 cals/kg). Beyond this age the growth rate decreases and the requirement per unit of body-weight drops accordingly.

Under 10 years the calorie requirements of boys and girls are considered to be the same. Above this age they are assessed at different levels. During the period of puberty and adolescence increased appetite is often very striking. Provided physical activity is high this increased appetite should be met by increased intakes of calorie-producing and other nutrients to levels often reaching those required by heavy-labouring adults.

Labourers in this country require relatively more calories than the American labourer since in the latter country greater use is made of labour-saving devices.

18. There is a growing view that gain in weight after maturity (25 years) is not physiological and should be avoided. The middle-age weight gain is largely due to an increase in the proportion of fat in the body and is not accompanied by a gain in active protoplasmic mass but may even be accompanied by a loss thereof. The reason for the decrease in active protoplasmic mass in middle-age may be partly endocrinological in origin, but is almost certainly due in part to decreasing activity; therefore, calorie intake should be reduced with advancing age. The recommendation of the Food and Nutrition Board of the USA for a reduction of 5% for each decade is accepted.[8] On this basis the average requirement for 35, 45, 55 and 65 years would be 95%, 90%, 85% and 80% respectively of the calorie requirement at 25 years.

Protein

19. The view that a person requires less protein than previously thought necessary is rapidly gaining ground.[9,10]. It is important however, that where the diet consists predominantly of cereals, such as wheat and maize, it must be supplemented by either animal foodstuffs or legumes, and that where maize is chiefly used, the protein standard must be slightly raised. In view of the importance of protein for body-building and functioning and for protection against tuberculosis and possibly other infections, it is advisable that the standard for the adult male should not be lower than 65 g., of which at least 1 3rd should be of animal origin, which can be partly replaced by protein from dry legumes. Dean[11] considers that a cereal-legume mixture may largely replace milk protein in the diet of children.

When calorie requirements are not met some of the protein is metabolized to provide the deficit, hence less is available for body-building, protection and regulation.

20. The protein requirement during the 3rd trimester of pregnancy and breast feeding is considerably higher and, because of the necessity to manufacture complete protein, the animal protein allowance is increased to 40% of the total.

21. In the child the requirement per unit of body-weight is higher than in the adult, and the quality of protein is of even greater importance. In the last decade it has been customary to recommend that the protein intake of a child under 1 year should be 3·5 g. per kg., or 1·6 g. per lb. of body-weight, expressed in terms of cow's milk protein. More recently, views expressed at a Conference on protein requirements (Josiah, Macy, Jnr. Foundation with FAO. and WHO. of UNO, June 19-24 1955, Princetown, New Jersey, (USA.) indicate that this figure may be unnecessarily high. The conclusions arrived at, and more especially the evidence on which they are based, are not available to the Committee. The suggested lower standards are also expressed in terms of cow's milk protein only and no equivalents are yet available for other animal proteins or for vegetable proteins. The Committee has, therefore, adhered to conventional standards.

Calcium

22. There is increasing evidence that the human body adapts itself to live economically and effectively at levels of calcium intake considerably lower than the usually recommended allowances.[3] In South Africa among the indigenous population, intakes are often 1/3rd of such allowances with no apparent ill effects. Unfortunately, there is no method of determining the level of calcium stores in the body. Furthermore, in strong contrast to other nutrients the intake of which is recommended here, there appears to be no evidence of any syndrome caused solely by calcium deficiency, or remediable by calcium supplementation only. To recommend allowances of a dietary constituent to protect against unspecified stigmata appears to be a questionable procedure. However, there is evidence from metabolic studies on well-nourished White people, that there is a tendency for a negative calcium balance to occur if the intake is below 10 mg. calcium per kg. of body-weight per diem. In the light of our present knowledge

it has been decided, therefore, to recommend this level of intake for the adult man and non-pregnant and non-lactating woman.[13]

The recommended calcium allowances in pregnancy and lactation are calculated from the amounts needed to supply the foetus and to maintain the calcium level in the breast milk. The standards for children have been calculated from the accretions of calcium in the body during growth as reported in the literature.

Iron

23. The precise requirements for iron are not well established but it is known that the incidence of iron deficiency or of hypochronic anaemia is higher in women than in men. If the intake of other nutrients is satisfactory there is no difficulty in obtaining the level of iron recommended. An additional 3 mg. per diem has been shown to be required during pregnancy. There is evidence that a considerable percentage of Bantu people receive a theoretical excess of iron in the diet from the use of iron pots.

Vitamin A

24. Vitamin A can be present in the diet in the form of its precursor carotene or as the active vitamin A. It will, therefore, be referred to either as carotene or vitamin A. One I.U. of vitamin A is equivalent to 0·3 micrograms of vitamin A alcohol or to 0·6 micrograms of β carotene. Owing to the uncertainty of the degree of conversion of carotene to vitamin A, it is desirable that a portion, perhaps as much as 1/3rd, should be present as vitamin A. When this is not practicable a more generous allowance of carotene is desirable.

Thiamin

25. The consensus of opinion seems to be that adults require a minimum of 0·23 mg. of thiamin per 1,000 calories. This standard is easily attained with diets containing unsifted or enriched cereal foods or an abundance of high-quality protein. It has been found that 0·35 mg./1,000 cal. is sufficient to allow of tissue storage.[13] Because of the greater demands of pregnancy and lactation the allowance should be slightly higher than 0·35 mg./1,000 cal. during this period. For children the thiamin allowance is also based on calorie intake. During puberty and adolescence an extra allowance is made to meet the higher physiological requirements.

Riboflavin

26. Although it has not been established that the requirement of riboflavin is related directly to protein requirement, it has been decided to adopt the NRC recommendation[2] of equating 0·025 mg. riboflavin per g. of protein.

Niacin

27. The metabolic pathways of tryptophane and niacin are intimately related. Although it is generally accepted that niacin requirements are approximately 10 times those of thiamin, these allowances have been increased because of the dietary pattern of the majority of the inhabitants of this country, whose tryptophane intake is apt to be low.

Ascorbic acid

28. Ascorbic acid is the most sensitive of the vitamins to oxidation and heat and a high percentage may be destroyed during transportation, storage and preparation of vegetables and fruit.

There is a close relationship between ascorbic acid and other nutrients, e.g. those responsible for tissue formation and maintenance and for development of the blood cells. Furthermore, the supply of ascorbic acid may be seasonal in parts of the country. The recommended allowances are, therefore, placed at levels higher than the Canadian figures, but considerably lower than those of the National Research Council[2] of the USA which have been regarded as unnecessarily high.[14]

Vitamin D

29. Vitamin D is essential for the absorption and metabolism of calcium and phosphorus. When there is reason to believe that exposure to sunlight is inadequate or that the sunlight is less active (as in the Western Cape during winter) a therapeutic intake of 400 I.U. per diem may be prescribed for infants and pregnant or lactating women. Extensive use of unrefined cereals containing phytic acid, which may interfere with the absorption of calcium, is an additional reason for vitamin D therapy.

Consideration of Nutrients not Tabulated

30. *Fat.* It is suggested that the fat level in the diet should be 20-30% of the total calorie intake, and for children, adolescents and, possibly, very active adults, it should constitute 30-40% of the calories. Under conditions of economic privilege there is a tendency towards undesirably high fat-intakes which, it is claimed, are potentially dangerous, at least in middle age and in sedentary occupations. According to some authorities the upper desirable limit for fat intake under these conditions is probably about 30% of the total calories. The possible requirement of the essential fatty acids (linoleic, linolenic and arachidonic acids) are easily covered where fat provides 20% or more of the calories.

31. *Carbohydrates.* Among Western populations, carbohydrate usually supplies less than half of the energy value of the diet. However, among the poorer sections of such populations, and also among tropical and semi-tropical populations generally, carbohydrate may contribute 3/4ths or more of the calorie requirements. Under such conditions, the present practice of refining cereals (the main source of carbohydrate) to produce a flour of improved appearance, palatability and keeping quality, is to be deplored. Not only is protein quality reduced, but there are losses of certain mineral salts and vitamins; in particular, thiamin is lost and this nutrient, together possibly with other nutrients, is essential for carbohydrate metabolism.

32. *Pyridoxine and the other members of the Vitamin B Complex.* No allowances have been made for these vitamins because it is considered that there should be no deficiency of other members of this group if adequate provision from natural sources is made for proteins and the B vitamins already mentioned.

The Dietary Standards Committee of the National Nutrition Council: F. W. Fox (Chairman), J. F. Brock, J. T. Irving, W. A. Odendaal, A. R. P. Walker, J. M. Latsky, A. J. du Plessis, L. J. Louw (Miss).

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CONTENTS

11. RECOMMENDATIONS ON CALCIUM NEEDS

The Group defined the *minimum requirement* of calcium for an adult as the smallest amount of that nutrient which will maintain health and keep the body in calcium balance over a period of years when the diet is otherwise adequate and the vitamin D status of the body is satisfactory.

The Group was conscious of the fact that such evidence as was available was not sufficient to allow it to specify a figure for the minimum adult requirement. The Group was not so much concerned with stating precisely the requirement of an individual, but rather with formulating its recommendations for the requirements of population groups. The conclusions reached on the question of calcium requirements were limited not only by the lack of evidence concerning the amount of the minimum requirement, but also by the fact that disorders and diseases attributable primarily to deficiency of dietary calcium have not been observed or reported in large populations subsisting habitually on intakes varying from 300 mg to 400 mg calcium per day. Some recent long-term balance studies have indicated that adults can adapt themselves successfully to an intake of calcium varying between 400 mg and 500 mg per day and even less. Such a range is higher than those observed in some parts of the world where no ill-effects attributable to calcium deficiency have been described. These bare facts, already considered earlier in this report, are reiterated as a prelude to a discussion of the question of requirements.

Suggested practical allowance

In view of the difficulty of defining quantitatively the minimum calcium requirement, the Group thought that the use of the term " average minimum requirement " was not justified in this report. It decided to recommend a range, rather than attempt to cite a single figure, in order to avoid giving an impression of accuracy which was not considered to be warranted in

the present limited state of knowledge. The recommendations with regard to calcium allowances are, therefore, based on different considerations from those which underlie the recommendations of the Committee on Protein Requirements (15). For these reasons, definition of such terms as "average requirement" and "optimal requirement" has not been attempted, although this was done by the Committee on Protein Requirements. The Group adopted instead the term "suggested practical allowance."

Suggested practical allowance is defined, for the purpose of this report, as the intake at which the needs of the great majority of persons in any defined population group are likely to be adequately met. It can, therefore, be considered a safe allowance. The possibility of undesirable effects on the health of a population with an average calcium intake habitually below this level should be borne in mind. Although knowledge gained from animal experiments may suggest the nature of such adverse effects, the symptoms and the possibility of their onset in man below any given level of calcium intake cannot be predicted with certainty.

Adults

In view of the scanty available evidence, a single figure for the lowest practical allowance could not reasonably be proposed. In the Group's opinion, intakes between 400 mg and 500 mg per day would represent the suggested practical allowance for adults. Since a lower intake of calcium is habitual in some large groups of populations in which no ill-effects attributable to calcium have been described, the Group was unable to conclude that the usefulness of raising an intake above the suggested practical allowance has been definitely proved.

The average intake of calcium in several countries is known to be considerably higher than 500 mg a day. Average intakes between 800 mg and 1,000 mg a day are found in some countries and of 1,000 mg to 1,500 mg a day in some population groups. The Group found no evidence that a daily intake as high as 1,500 mg was undesirable. It, therefore, did not suggest alteration in the calcium intake of large groups of people whose dietary habits provide such a level. The Group, however, was of the view that raising the calcium intake beyond one gram was unlikely to serve any physiologically useful purpose.

The scarcity of available information (see Chapter 3) did not allow the Group to make any suggestions about the upper limit of calcium

intake beyond which signs and symptoms of toxicity would supervene. In this respect, individuals with special susceptibility, such as those liable to kidney stone formation, may require special consideration.

Children and adolescents

Recommendations of allowances for nutrients during the growing period from infancy through adolescence have to take into account the needs not only for maintenance but also for continued accretion of calcium for purposes of skeletal growth. Unfortunately, a great deal of uncertainty exists about the rate of skeletal growth in children. The rate of growth, as judged by changes either in weight or in height, is not constant during the whole growth period. Weight and height increase rapidly during the first year of life. During the succeeding eight to ten years, prior to puberty, weight increase is relatively slow and gain in height is relatively greater than that in weight during this period. Also, the percentage of calcium in the body is greatly augmented (from approximately 0.8 percent at birth to approximately 1.7 percent in adulthood) during the growth period.

Many calculations of the expected annual increment in calcium required to produce the adult skeleton have been made (32), the most recent being that of Leitch and Aitken (36). In the latter, the authors assume the increment in calcium to be proportional to the increase in weight and also that the proportional increase of calcium in the body parallels the gain in body weight. Such calculations postulate the need for a high intake of calcium to provide for the growth spurt at puberty. On the other hand, increase in height follows a pattern quite distinct from that of weight and it may be equally logical to relate calcium needs to changes in height. The Group, in view of these considerations and aware of the evidence of reasonable growth in children on relatively low calcium diets, felt that the division of the growth period into several age groups would be unwise. Moreover, for reasons discussed earlier, it was decided to recommend a range of suggested practical allowances, instead of a minimum requirement, as follows:

Age	*Suggested practical allowances (mg per day)*
0 to 12 months (not breast fed)	500 to 600
1-9 years	400 to 500
10-15 years	600 to 700
16-19 years	500 to 600

It has been assumed that the adequately breast-fed infant receives sufficient calcium for its needs. The amounts recommended for artificially fed infants are based on the lower of those values found in the current feeding practices of western countries. The Group realized that children and adolescents may have an intake of calcium higher than that indicated above, even reaching a level of 1,500 mg per day, depending upon age, food habits and other factors. In the opinion of the Group the available evidence does not indicate that such a high intake is undesirable, as already stated in an earlier section (p. 11). No suggestion was made, therefore, for any alteration in the current dietary practice involving such intakes.

Sex

The Group was of the opinion that there was no evidence for recommending different allowances for boys and girls, or for adult males and nonpregnant and nonlactating women.

Pregnancy and lactation

The growth of the fetus, particularly during the last trimester of pregnancy, may require about 30 g of calcium. Additional drain on the maternal organism occurs during lactation. The daily output of breast milk has been assumed as 850 cc, as in the earlier reports of the Committees on Calorie and Protein Requirements. On this basis, approximately 300 mg of calcium a day will be needed by the body. Given a lactation period of six months, the additional calcium need may amount to about 50 g, and this would increase if lactation continued for a longer period. The total additional calcium requirement in pregnancy and lactation together would thus be between 80 g and 100 g or even more, depending upon the amount of milk produced. Taking into consideration also the possibly more efficient utilization of dietary calcium during lactation, the Group concluded that the suggested practical allowance should be between 1,000 mg and 1,200 mg per day. An intake within these limits should be provided during the third trimester of pregnancy and throughout the period of lactation. The Group realized, however, that in certain populations, successful repeated pregnancies and lactations are achieved with a calcium intake much below the suggested allowance. Extensive observations to determine if any demonstrable ill effects on the health of the mothers occur under such conditions are obviously needed.

Old age

Certain recent work suggests that an inadequacy of dietary calcium may be one of the causes of senile osteoporosis, a condition which has been found to be fairly common in some countries in individuals over 60. However, the available evidence was not considered sufficient to permit the assessment of any special allowance for this age group. This question should be reviewed after the results of further research become available.

Physical activity

The Group did not recommend additional intake of calcium with respect to physical activity because of the lack of relevant evidence that such is needed.

12. RECOMMENDATIONS FOR FUTURE RESEARCH

It is readily apparent from the preceding chapters of this report that definitive information upon which calcium requirements can be based is extremely limited. As indicated in the Introduction, the Group considered it useful to emphasize the inadequacy of the data available in the hope that appropriate research may be stimulated as soon as possible. Direct human studies should be the most useful; in particular, the "natural experiments" provided by large population groups consuming different amounts of calcium should be adequately utilized. However, much of the information required can be obtained only with experimental animals, and such studies should be encouraged. The Group wishes to call special attention to the desirability of encouraging studies on the various subhuman primates, since their nutritional requirements may be more analogous to those of man than to the requirements of some of the other laboratory animals in common use.

Composition of the human body with special reference to calcium

Information is needed on the total calcium content and the proportion of calcium and other constituents in the human body. Data should be collected on different population groups with regard to age, race and diets differing in calcium content.

Studies on bone

1. Basic studies on the histology, biochemistry and physics of bone and the influence of age and diet should be encouraged.
2. The Group particularly recommends that co-operative efforts be made for the collection and thorough examination of bones from all age groups in different regions of the world. Particular attention should be given to those bones which are known to have a high rate of calcium turnover, such as the vertebrae.

Food consumption and composition with special reference to calcium

1. The assessment and formulation of nutrition programs requires knowledge of the level and patterns of food consumption.

2. Accurate information is required on the composition of food *as eaten*. Inasmuch as there are interrelations between calcium and other nutrients, the analysis should not be limited to calcium alone. It should be noted that the introduction of new strains and of new agricultural practices may change the composition of foods. Thus food analysis should be a continuous effort.

3. Particular attention should be paid to unusual sources of calcium both in dietary surveys and in studies on food composition. These include the water supply and certain methods of food processing, as well as those foods which have a naturally high calcium content.

4. The Group was not impressed with the likelihood that the nature of the diet will markedly affect calcium requirements. Nevertheless, studies on the availability of calcium in foods should be encouraged. In this regard, it would be useful to formulate a standard reference diet to provide a common base line of comparison for studies in different laboratories.

Determination of minimum calcium requirements

1. Long-term balance studies, in which the calcium intake should be deliberately varied, need to be done both on children and adults with different nutritional backgrounds.

2. Investigations on the methodology used in balance studies would be useful. Particular attention should be paid to the assessment of the magnitude of the errors in such studies; and the possibility of improving and simplifying procedures, for example by the use of fecal markers, deserves attention.

3. Adequately designed growth and balance studies should be undertaken on children. Populations living on low calcium diets are the most appropriate experimental subjects and differences in calcium intake should be the sole variable insofar as this can be achieved.

4. The effects of repeated pregnancies and long lactations should be determined in the women of different population groups in relation to the varying levels of calcium in their customary diets.
5. The influence of physical activity on calcium balance and calcium requirements requires investigation.

Determination of the maximum tolerated dietary levels of calcium

The difficulties of defining minimal needs are also encountered in defining maximum tolerated levels of calcium. In view of the large amounts consumed by some individuals and population groups, additional studies on both man and experimental animals should be undertaken in this field. Particular attention should be given to the possible importance of inter-relationships between the intake of calcium and that of other dietary constituents.

Population studies

Attention has already been drawn to the necessity of extensive study of those population groups habitually consuming very high or very low levels of calcium. The Group wishes to re-emphasize the importance of such studies utilizing modern metabolic, clinical and histologic methods.

Physiology and biochemistry of calcium metabolism

An adequate appreciation of the role of dietary calcium in health and disease requires a thorough understanding of calcium metabolism. The Group recommended that additional efforts be made in the following areas:

1. study of the factors and mechanisms involved in the absorption of calcium and its re-excretion;
2. definition of the magnitude of endogenous calcium excretion under various conditions;
3. determination of the relationships between calcium intake and the level of calcium in the plasma and other plasma constituents which may influence this relationship; this is particularly important in view of the evidence that certain populations on habitually small intakes of calcium have lower levels in the plasma;

4. study of the magnitude and factors controlling dermal losses of calcium;
5. investigation of mechanisms and factors controlling the "adaptive" process;
6. continuing study of the interrelations between dietary calcium and other elements, particularly with regard to iron, magnesium and the trace elements.

Disorders and diseases involving calcium

Those conditions in which calcium metabolism is known or suspected to be abnormal require extensive study utilizing all the appropriate epidemiological, clinical, histologic and biochemical methods. Such studies are justified in their own right and may contribute significantly to knowledge of normal calcium metabolism. Attention is called specifically to the need for study of:

1. the role of calcium intake in the etiology and treatment of senile osteoporosis;
2. calcium intake in relation to renal stone formation;
3. other clinical conditions which may result from an excess or deficiency of dietary calcium;
4. the etiology of those diseases which involve soft tissue calcification;
5. specific pathologic conditions in which an intake beyond the recommended limits may be advisable.

Tests of calcium deficiency

Increased efforts should be made in the search for methods of detecting calcium deficiency or for the evaluation of nutritional status with regard to calcium. Improved radiologic techniques offer some promise, and methods for the biochemical evaluation of calcium in the blood, tissues and excreta should be improvised.

Influence of dietary calcium on radiostrontium retention

Further long-term research is needed to determine the role of dietary calcium in the absorption and retention of radiostrontium under varying dietary conditions and at different ages.

Priorities in research

The results which will be obtained from specific research proposals can seldom be predicted with certainty. Nevertheless, there are some areas of research particularly relevant to the establishment of calcium requirements which appear more likely to yield significant practical results in the near future than others. The Group wished to reiterate those which, in its opinion, fall into this category and thus deserve emphasis, though the items listed are not in order of priority:

(*a*) basic studies on the histology, biochemistry and physics of bone in relation to age and growth;

(*b*) the collection and examination of bones from different regions, especially those bones, such as the vertebrae, which have a high rate of calcium turnover;

(*c*) the relationship between calcium intake and calcium balance and growth;

(*d*) thorough study of population groups habitually consuming very high or very low levels of calcium;

(*e*) the relationship between calcium intake and level of calcium in the plasma and other plasma constituents, such as proteins, which may be influential;

(*f*) the effects of different levels of calcium intake on health in repeated pregnancy and lactation;

(*g*) the role of dietary calcium in the etiology and treatment of osteoporosis.

Appendix 5

LIST OF PARTICIPANTS

MEMBERS

Professor C. E. DENT	Department of Medicine, University College Hospital Medical School, London, England
Professor R. W. ENGEL	Head, Department of Biochemistry and Nutrition, Virginia Polytechnic Institute, Blacksburg, Va., U.S.A.
Dr. D. M. HEGSTED	Associate Professor, Department of Nutrition, Harvard University School of Public Health, Boston, Mass., U.S.A.
Dr. S. K. KON	Head, Department of Nutrition, National Institute for Research in Dairying, Shinfield, Reading, England
Dr. A. NELSON	Chief, Division of Medicine, Research Institute of National Defence, Sundbyberg, Sweden
Professor R. NICOLAYSEN	Director, Institute for Nutrition Research, University of Oslo, Blindern, Norway
Dr. P. Royer	Professeur agrégé à la Faculté de Médecine, Paris, France
Dr. H. K. STIEBELING	Director, Institute of Home Economics, Agricultural Research Service, U.S. Department of Agriculture, Washington, D.C., U.S.A.

Dr. M. SWAMINATHAN	Head, Division of Dietetics, Central Food Technological Research Institute, Mysore, India
Dr. R. TARJAN	Director, Nutrition Institute, Budapest, Hungary
Dr. A.R.P. WALKER	Human Biochemistry Research Unit, South African Institute for Medical Research, Johannesburg, South Africa
Professor F. G. YOUNG (Chairman)	Department of Biochemistry, University of Cambridge, England

FAO

Dr. M. AUTRET	Director, Nutrition Division
Dr. H. D. CREMER	Chief, Applied Nutrition Branch, Nutrition Division
Dr. K.K.P.N. RAO	Chief, Food Consumption and Planning Branch, Nutrition Division

WHO

Dr. V. N. PATWARDHAN	Research Officer, Nutrition Unit
Dr. S. K. REDDY	Nutrition Unit

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CORRESPONDENCE

CALCIFICATION IN THE SOUTH AFRICAN BANTU

To the Editor:—I read with interest the recent contributions of Dr. Stearns on the requirement of calcium (*J. A. M. A.* **142**:478 [Feb. 18] 1950) and of Professor Youmans on the subject of calcium deficiency (**143**:1252 [Aug. 5] 1950). The need of a high intake of this element has often been emphasized, and it has been stated that in the United States the diet is more likely to be deficient in calcium than in any other element. Yet Professor Youmans maintains that the incidence of calcium deficiency is unknown, and Professor Snapper (in Joliffe, N., and others: Clinical Nutrition. New York, Harper & Brothers, 1950) considers primary deficiency of calcium to be extremely rare. Since misgivings prevail over the level of the calcium intake of a relatively well fed population, such as that of the United States, the question arises as to the state, in terms of calcium deficiency diseases, of the many millions of people in other parts of the world whose diet is greatly inferior in calcifying properties.

In South Africa the calcium intake of the Bantu, especially the town dwellers, can seldom exceed 0.5 Gm. per day. The phosphorus intake, much of it in the form of phytic acid phosphorus, is high, usually more than 1.5 Gm.; moreover, at the times and in the places where maize is the exclusive source of calories, a calcium-phosphorus ratio as unfavorable as 1 to 10 is reached. Practically no vitamin D is ingested.

The present situation, in the light of the information available, is as follows. In East Africa, the Rhodesias and South Africa, rickets is reported to be rare. But the disease is common where urban Bantu are overcrowded, just as it is common in India under the same conditions. In Johannesburg, it occurs more frequently in babies less than a year old, who are mainly breast fed; but it is of rare occurrence after the age of 2. Tetany is considered by experienced clinicians to be uncommon. Bantu mothers are reported not to suffer from osteomalacia. The calcium content of their breast milk, for the few samples examined, has been found to lie within the same range as that of European mothers. Regarding serum levels for calcium and phosphorus, the limited number of determinations carried out suggest that the Bantu have the same or only slightly lower values than Europeans. Ample opportunity for radiologic observation is afforded by many hospitals, for example, those concerned with the quarter of a million Bantu workers employed in the gold mines of the Witwatersrand. The opinion is held that there is no difference in calcific density between the bones of these people and of contemporary Europeans. It is averred that fractures are not unduly liable to occur; there is evidence, moreover, that when these do occur, the rate of healing is, if anything, more rapid than is the case with Europeans. In general, the rural Bantu, when consuming their traditional high cereal diet, have a low incidence of caries, but, as has been reported of primitives elsewhere, when the Bantu adopt European food habits, deterioration begins to take place. The average height of the Bantu is certainly less than that of European South Africans, but, since their diet is frequently unsatisfactory in many respects, not only on account of their low intake of calcium, it is unfair to blame a deficiency of this element as the sole cause. It is of importance, however, that poor European South Africans consume a diet similar to that of the Bantu, yet, reports indicate that the height of the children is not adversely affected thereby. It might also be added that there is evidence that European South African children are, with minor limitations in certain age groups, taller and heavier than their contemporaries in Great Britain, Canada and the United States; yet, their intake of calcium, in general, is below that in the above countries. The very important factor favoring calcification is the sunlight in this part of the world. Can the lack of deficiency stigmas be wholly attributed to this factor?

The information given requires further investigation before being firmly established; to this end, cooperative research work, biochemical, radiological and clinical, is proceeding. Should the above observations be confirmed, the conclusion would seem to be inescapable that, at least where sunlight is plentiful, the critical importance attached by nutritionists to a high intake of calcium is unwarranted.

(This letter is published with the permission of the South African Council for Scientific and Industrial Rsearch.)

A. R. P. Walker, Ph.D.,
Nutrition Unit, Council for Scientific and Industrial Research, South African Institute for Medical Research, Johannesburg, Union of South Africa.

ROBERT LATOU DICKINSON

To the Editor:—Few persons have contributed more to the art and science of obstetrics in the United States than Dr. Robert Latou Dickinson, and we cannot let the moment of his passing go by without recording our appreciation of him as a great person, doctor, teacher and artist. He was one of the first to warn against the evils of "assembly line obstetrics" to the personality of the mother and father in the normal function of childbearing and to decry the growing trend to make birth a surgical operation.

When Dr. Dickinson retired from active medical practice, he made in the last two decades of his life a unique and important contribution to medical and health teaching. Working with Abram Belskie, a sculptor of great talent, the two developed medical teaching aids in plaster and rubber. The first of these were made for the Maternity Center Association's New York World's Fair exhibit. They depicted in life-size sculptures the development of a baby from the moment of fertilization to the moment of birth. These sculptures were one of the most popular exhibits at the Fair and were later made into a medical teaching book, the "Birth Atlas," which is used in the medical and nursing schools and parents' classes in many countries of the world. Copies of these sculptures are now on exhibit in the New York Museum of Natural History, the Field Museum in Chicago, the Cleveland Health Museum, the Dallas Health Museum and in a number of foreign countries. The rubber models were developed to help the student doctor and nurse and the parent to learn more about the normal human body. Dr. Dickinson's books on a number of subjects related to human reproduction are of worldwide repute. His fearless willingness to take a public position on subjects of controversy won for him the admiration not only of those who agreed with him but of those who disagreed.

I speak for the board, the medical board and the staff of the Maternity Center Association when I say that his passing is an irreparable loss to the dynamic advances in our field of endeavor. But his contribution to medical science and to human relations, especially in the development of mutual understanding between the doctor and his patient, will live forever among the people of America.

Mrs. Shepard Krech, President,
Maternity Center Association,
New York, 21.

DRINKING WATER AS A SOURCE OF CALCIUM

by

A. R. P. WALKER

(Nutrition Unit, South African Council for Scientific and Industrial Research at the South African Institute for Medical Research, Johannesburg).

The Functions of Calcium

The more important physiological functions of calcium may be summarized briefly as follows:—

1. It is essential for the calcification of bone and teeth.
2. It is necessary for the adequate contraction of heart muscle.
3. It regulates the excitability of nerve fibres and centres.
4. It is essential for the clotting of blood.

The biological importance of this element is therefore obvious.

Standard of Intake

Evidence is accumulating from the results of calcium blanche studies carried out by independent observers, that an allowance of 10 mg. calcium per kg. body weight, is sufficient to meet the body's requirement; an average man of 70 kg. would thus need 0·7 g. daily. The present orthodox standard is more liberal; for adults, the South African National Nutrition Council has recommended a daily allowance of 0·8 g. A higher level of intake is, of course, essential for growing children, and for pregnant and lactating women.

Availability for Consumption

The following figures indicate the approximate amount and current cost of different foodstuffs required to furnish 0·8 g. calcium:— milk, 1·2 pints, 6½d.; cheese, 3 ozs., 5d.; eggs, 2 doz., 4s. to 9s.; bread, 5 to 6 lbs., 1s. 6d.; haricot beans, 14 ozs., 7d.; green peas, 5 to 6 lbs., 1s. 6d. to 3s.; cabbage, 4 to 5 lbs., 1s. to 2s.; maize (straight run), 9 lbs., 1s. It will be observed that, apart from milk and cheese, substantial amounts of all these foodstuffs would have to be consumed to meet the body's daily requirement of calcium. The availability and price of milk and cheese are thus the governing factors where the level of calcium intake is concerned. It has been calculated that if the population of the United States, already probably the best fed of any country, were to adopt the Stiebling liberal allowance dietetic standard (which allows for the consumption of about 1·2 pints of milk daily for each person), an additional 15 million cows would be needed! In South Africa, recent nutritional surveys and reports have indicated that Europeans of the lower income groups, also the Asiatics, Coloureds, and Bantu, are at present subsisting on diets having a calcium content appreciably lower than the current accepted standards. In view of such evidence, McLester [1944] considers that for the present (and doubtless for a long time to come), the diet of most people the world over is more likely to be deficient in calcium than any other element. In consequence of this state of affairs, every dietetic source of calcium capable of contributing a significant amount of this element, becomes of increasing importance.

The Calcium in the Drinking Water

The drinking water is a frequently overlooked source of calcium. The amount of this element ingested depends on many factors: on the total amount of water consumed; its calcium content; the proportion of raw and boiled water consumed, also the temporary and permanent hardness of the water; finally, it is essential to consider the availability for metabolism of the inorganic calcium ingested. These factors will now be considered in turn.

The amount of water consumed daily.

Water consumption varies widely from person to person; the figures obtained must therefore be regarded as approximations, and only applicable to individuals leading a very moderately active life.

The amount of water consumed daily may be classified under the following headings:—

1. Raw water, consumed alone, or in home-made soft drinks.
2. Boiled water, as in tea, coffee, and other beverages.

3. Water added in the preparation of cereal products, such as bread, porridge, and occasionally, cereal puddings.
4. Cooking water which is not decanted, as in soups, stews, and stewed fruit.
5. Cooking water, the major portion of which is discarded, as in the cooking of vegetables.
6. Water in milk, alcoholic drinks, and so forth.

The proportion yielded by each of these sources will now be discussed in detail.

1. *Raw Water.* In general, for the type of individual considered, water consumed in the raw state forms a comparatively small proportion of the total water drunk. Magee [1937], in studying the daily water consumption habits of the inmates of two institutions in Great Britain, found that on the average, about a small cupful per day was consumed. In South Africa, Walker, Fox, and Irving [1947], from data obtained during long-term mineral balance experiments, found that two subjects consumed slightly more than this amount, but it seldom exceeded 200 ml. daily.

2. *Boiled Water.* When water is boiled, some of the calcium carbonate and bicarbonate accounting for the temporary hardness, is precipitated. If just brought to the boil, little precipitation occurs; but should boiling be allowed to continue, especially in a well-"furred" kettle, the amount deposited is greatly increased. Moran and Hutchinson [1942] consider that on the average, only half of the temporary hardness calcium reaches the tea or coffee pot. More recent experiments by McCance and Widdowson [1943] support this view. The average daily total intake of water was considered by Starling [1933] to be of the order of 1450 ml.: if, say, 150 ml. is allowed for a small cup of unboiled water, this leaves a boiled water consumption of 1300 ml. Magee [1937] found that the boiled water consumption in the above institutions was about 1500 ml. daily. Observations by Walker, Fox and Irving [1947], for the two subjects referred to, tend to confirm this figure. For purposes of calculation therefore, the boiled water consumption will be taken as 1500 ml. per head daily.

3. *Water added in the preparation of cereal products.* (a) Bread. From the Family Budget Enquiry Report [1936-7], the average daily consumption of bread may be taken as 12-14 ozs. per head: in the making of the dough, roughly 100 ml. of raw water is incorporated. (b) Other cereal foods. The above Report indicated that the combined consumption of oats, rice, and mealie meal, is fairly constant in the middle and lower income groups, approximating to 3 ozs. daily. In the preparation of these foodstuffs for eating, roughly 250 ml. tap water is added. The consumption of cereal products thus involves the ingestion of the calcium present in about 350 ml. of raw water.

4. *Water in soups, stews, stewed fruit, etc.* Walker, Fox and Irving [1947], found that the order of 100 ml. was the average daily amount of water consumed with these foods, for the two subjects under long-term observation.

5. *Cooking water in vegetables.* McCance and Widdowson [1943] compared the calcium content of peas and potatoes when cooked in distilled water, and in the comparatively soft Cambridge tap water: they found that the tap water increased the calcium content; since, however, the increase did not amount to more than a few milligrams, no allowance will be made for this phenomenon in the following calculations.

6. *Water in milk, alcoholic drinks, etc.* The consumption of milk and alcoholic drinks, especially the latter, is subject to extreme variations; but since tap water is not concerned in their immediate origin, they will not be taken into account.

Summing up, the raw water consumption may be regarded as being made up of: water drunk, 150 ml.; from cooked cereal products, 350 ml.; from soup, etc., 100 ml., making a total of 600 ml. daily: for purposes of calculation, this figure will be reckoned as 500 ml. The boiled water consumption has been shown to be of the order of 1500 ml. daily; this makes a total of 2000 ml. tap water consumed daily. It must be repeated that these figures are only likely to apply to adults leading a very moderately active life.

Calcium ingested from British drinking waters.

Table I illustrates four representative British waters. Using data given by Suckling [1945], the amounts of calcium ingested, employing the above water consumption figures, have been calculated; it has been assumed that half the temporary hardness calcium of the boiled water is lost during boiling.

Moran and Hutchinson [1942] consider that an average figure of about 75 mg. calcium is

TABLE I

Calcium ingested from various British drinking waters.

	Tunbridge Wells, Kent.	Lambeth, London.	Sydenham, London.	Bedford.
Total Hardness, calcium and magnesium salts as $CaCO_3$ per 100,000	4	20	28	38
Total calcium, as mg. Ca per 100 ml.	0·9	5·1	10·7	14·0
Total calcium ingested (mg.)	17	63	134	175

TABLE II

Calcium ingested from South African drinking water (ground waters).

	Very pure waters.	Slightly saline chloride waters; temporary hard carbonate waters; sodium carbonate waters.	Highly mineralized brak waters.
Total Hardness, as $CaCO_3$ per 100,000 ...	1—5.5	11—28	41—106
Total calcium as mg. Ca per 100 ml ...	0·2—0·9	1·8—7·5	5·4—17·7
Total calcium ingested (mg.)	2—10	27—95	90—300
European consumers (approx.)	650,000	1,250,000	350,000

TABLE III

Estimate of calcium ingested daily from the drinking waters of the main centres of population.

	Approximate population (1941).	Total hardness $CaCO_3$ per 100,000.	Calcium content mg. per 100 ml.	Estimate of calcium ingested daily (mg.).
Rand Water:				
Vaal River (T)		8·5	2·2	31
Zuurbekom		12·5	2·5	26
Cape Town*	188,000	1·0	0·14	2
Pretoria:	113,000			
Fountains		20	4·3	54
Rietvlei (Springs)		11	2·3	29
Rietvlei		12	2·5	31
Durban (T)	113,000	4·8	0·14	2
Port Elizabeth	58,000	5·2	0·9	14
East London (T)	35,000	23		
Bloemfontein (T)	33,000		2·1	26
Kimberley (T)	17,000	9·6	2·95	45

*Cape Town is now being supplied with "white" water of much greater hardness.
(T) ★ Treated water supply.

contributed daily by the drinking water of Great Britain.

Calcium ingested from South African drinking water.

In South Africa, there are many different types of water, ranging from the exceedingly soft waters of the Table Mountain Series to the highly brak waters in the North-West Cape Province. Table II has been compiled from data given in Bond's monograph [1946] on the water supplies of the Union of South Africa.

The approximate number of European consumers in each group was calculated by making use of Bond's data and maps, and also the population data from the Union Year Book and recent census reports.

From this table, it may be observed that:—

1. In just under a third of the Union's white population, the calcium contributed by the drinking water is negligible.
2. In a little less than half of the population, the average daily calcium intake from the water is about 60 mg., i.e. much the same as the estimate of Moran and Hutchinson for Great Britain as a whole; the contribution may be regarded as having some nutritional benefit.
3. In less than a sixth of the white population, the calcium ingested with the drinking water, 100-300 mg. daily, is of considerable nutritional importance. Such an amount might well make all the difference between a calcium intake that is deficient, and an intake that is adequate for maintenance. It should be mentioned that these highly saline waters, apart from certain exceptions, are not outstandingly harder than an appreciable number of British drinking waters mentioned by Suckling [1945].

The contributions afforded by the drinking waters of the larger South African centres of population may be of interest, and are given in table III.

Availability for metabolism of drinking water calcium.

The calcium in the drinking water may be present as bicarbonate, sulphate, or chloride.

Dealing firstly with evidence from experiments on rats, Tisdale, Drake and Herbert [1938], showed that when using the carbonate, chloride, phosphate, gluconate, and lactate of calcium, also whole milk powder, Casec, and Pablum, the percentage of added calcium retained was essentially the same in each case. Lunde and Lie [1940], found that the calcium of fish bones (present as phosphate and carbonate), was just as available to the organism as milk calcium.

With humans, Stearns and Jeans [1934-5] found that insoluble tri-calcium phosphate was utilized by children as well as water-soluble calcium salts. Kempster, Breiter, Mills, McKey, Bernds and Outhouse [1940], found that boys and girls utilized the calcium of dicalcium phosphate as readily as milk calcium.

It is therefore highly probable that the calcium in drinking water is as available to the body for metabolism as the calcium contained in milk.

Summary

1. Due to the cost and frequent scarcity of milk and cheese—foods rich in calcium—it is possible that the diet of the general public is more likely to be deficient in this physiologically important element than in the case of any other element.
2. One frequently overlooked source of calcium is the drinking water. A person of very moderate activity consumes roughly 500 ml. raw water, and 1500 ml. boiled water daily, from all sources. Using these figures, it has been estimated that:—
   (a) About a third of the white population of the Union, derive a negligible contribution of calcium from their drinking water.
   (b) About half of the population benefit by an average of roughly 60 mg. calcium daily, an amount of some nutritional significance.
   (c) The remainder, about one-sixth, consuming highly saline water, ingest 100-300 mg. calcium daily, a contribution of considerable nutritional importance.
3. The calcium in the drinking water is considered to be as available for metabolism as the calcium in milk.

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OSTEOPOROSIS AND CALCIUM DEFICIENCY.

ALEXANDER R.P. WALKER M.Sc., Ph.D.*

Within recent years there has been an increasing interest in osteoporosis (post-menopausal and senile) with regard to its features, occurrence, causative factors, and treatment.

Briefly, the disease is characterised, roentgenologically, by rarefaction of bone. There is a reduction of bone mass or mineral matter per unit volume (involving generalized loss of spongiosa and inner layers of cortex), without change in percentage composition. In this respect, it differs from rickets and osteomalacia which, although also marked by bone rarefaction, are associated with a reduction in percentage mineral composition. The most obvious sequela of osteoporosis is pathological fracture of vertebrae, femura, or ribs. The disease is common in Whites. It affects females more than males, both numerically and in severity. From surveys undertaken mainly in the United States, it is believed that 10 - 50 per cent of people over 65 years are severely osteoporotic: it has been calculated that there are approximately four million of such people in the U.S.A.[1]

Earlier workers, partly on the basis of animal studies, considered that a deficiency of calcium was implicated.[2,3] Later, Albright and Reifenstein[4] attached chief blame to diminished estrogen production in old age, thus leading to decreased formation of the protein matrix bone. It was believed that depletion of bone arose because its rate of formation was retarded, while the rate of resorption was unaffected. In support of this conception, it has been claimed that supplements of estrogens relieve pain in a proportion of cases,

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From the Human Biochemistry Research Unit, South African Institute for Medical Research, Johannesburg, South Africa, and the Council for Scientific and Industrial Research, Pretoria, South Africa.

*Head, Human Biochemistry Research Unit.

improve calcium retention, arrest the osteoporotic process, and reduce proneness to fractures. At present there is a trend to revert to the view that a sustained deficiency of calcium bears main aeticlogical responsibility.[1,5-17] It is believed that often, although not invariably,[17,18] subjects with osteoporosis either have a relatively low intake of calcium, or are poor absorbers, or high excretors of the element. In consonance, it has been reported that the tissues of sufferers have an avidity for the element, that calcium supplements reduce proneness to fractures, and frequently ameliorate pain. Until recently, neither form of treatment (i.e. sex hormones or calcium salts) has been reported to result in roentgenological improvement. Two current reports, however, claim improvement in a proportion of cases.[15,16] It should be added that some groups of workers believe that both hypotheses have a measure of validity and that both treatments are more effective than either given alone.[1,10,13,17]

If the calcium deficiency hypothesis is valid (and this is the issue with which this paper is primarily concerned), then in corresponding age groups, it would be possible to demonstrate, epidemiologically, the existence of a correlation between level of calcium intake and frequency and severity of osteoporosis. The correlation, however, will be vitiated if factors other than calcium intake, such as race and activity, are of profound importance in the aetiology of the disease. Little endeavour, however, has been made to enquire into or to discuss whether such a correlation actually obtains.

Nordin[20] believes that there is a measure of analogy between iron deficiency and iron deficiency anaemia, and low calcium intake and osteoporosis. In a given population, knowing the level of iron intake, the composition of the diet, and the frequency of infections prevailing, it is possible broadly to predict the prevalence and extent of the iron deficiency anaemia likely to occur. In a comparable situation, knowing the level of

habitual calcium intake, is it equally possible to predict the prevalence of osteoporosis? Consider the following situations:-

1. In Glasgow (the home of so much recent research on osteoporosis and earlier research on rickets), forty to fifty years ago, poverty was widespread. Half of the population lived in 1 room dwellings, and over 90 per cent in 1 or 2 room dwellings.[21] Calcium intake undoubtedly was much lower than at present. Hence, in the elderly, there should have been much more osteoporosis at that time compared with nowadays.

2. During World War II, for many years the inhabitants of several countries had a reduced intake of calcium. Although the period of privation was not long, the lower intake should have aggravated the frequency and sequelae of osteoporosis.

3. Since calcium intake, within limits, rises with increase in income, osteoporosis should be encountered more frequently among those in lower compared with upper socioeconomic classes. Thus, the disease should be commoner in the poorer North of Britain than in the more prosperous South. Comparing countries, the prevalence of the disease in less privileged regions in Central and Eastern Europe should be greater than in countries such as the United States, Britain, and Scandinavia. Finally, and in particular, if calcium intake be of predominant importance, osteoporosis should be <u>far</u> commoner, indeed, almost ubiquitous among the elderly in the indigeous populations of Africa, the Middle and Far East, compared with Western populations.

There is some evidence that groups of White subjects with osteoporosis have a lower mean calcium intake compared with that of groups of "normal" subjects without obvious evidence of the disease.[1,5,6,10,11,16] Nevertheless, to the writer's knowledge, there is no unequivocal evidence on random contrasting populations in any of the three situations enumerated above which has demonstrated a significant inverse correlation to obtain between level of calcium intake and prevalence of osteoporosis. Absence of appropriate evidence, of course, does not necessarily imply that there is no correlation; but its absence is of significance bearing in mind the wealth of information available on deficiencies of other dietary components and the respective malnutritional stigmata.

An enquiry into the validity of the calcium deficiency hypothesis may be approached by two avenues:-

1. By selecting a population known to be accustomed to a low calcium intake (such as the South African Bantu) and examining whether osteoporosis is or is not common in the elderly.

2. By seeking to determine whether the accepted criteria of a deficiency disease are satisfied, namely, the presence of (a) deficient intake, (b) specific stigmata, and (c) therapeutic or prophylactic response to the addition of a specific nutrient or nutrients.

These two approaches will now be explored.

CALCIUM INTAKE AND OSTEOPOROSIS IN THE SOUTH AFRICAN BANTU

Calcium intake. On the South African Bantu we have determined the calcium concentration of (1) samples of foods and drinks, including water, as consumed by them; (2) their foodstuffs as cooked

in the laboratory; (3) 24-hour urine collections of children and adults, also numerous random samples of urine, on which calcium/creatinine ratios[22] have been determined; (4) stools collected from urban and rural areas, reckoning calcium content on the basis of an excretion of 70 g. dry faeces per diem (common to Bantu adults on a high residue diet[23]). Combined results of all these studies indicate that only a small minority of Bantu, say, 10 - 15 per cent, are accustomed to daily intakes of calcium of more than 500 mg. This assessment is in harmony with other information obtained locally.[24-27] In Britain, in striking contrast to the foregoing, Nordin considers that 95 per cent of the population have an intake exceeding 500 mg. per diem.[6]

The low calcium intake situation depicted in the Bantu, moreover, is aggravated by the following considerations:-

1. Among rural groups, we have found that the average number of children to each mother is about six. We do not know the calcium content of Bantu infants; however, allowing 25 g. calcium per foetus, the loss of calcium from six pregnancies is about 150 g. Prolonged lactation is usual; the mean calcium concentration of breast milk is normal (28 mg.%[28]); hence for, say, 9 months of lactation, the drain of calcium for 5 children (allowing for one early death) amounts to about 300 g. Admittedly, in urban areas, families are smaller and breast feeding curtailed. Nevertheless, by far the major proportion of Bantu mothers must lose about 400 - 500 g. calcium from their several pregnancies and long lactations. This amount may well be equivalent to at least half of their total body calcium. In comparison, White mothers with 2 - 3 pregnancies and lactating, say, for 3 months, lose 100 - 150 g. Thus, this physiological loss of calcium is about three times heavier in Bantu compared with White mothers.

2. At meal time it is traditional for the African male to receive preferential treatment; the pregnant and lactating mother seldom receives special consideration, indeed, in some ethnic groups, certain nourishing foods are taboo.

3. Under the climatic conditions prevailing, such losses of calcium as occur from sweating are likely to be greater in Bantu than in Whites.[29,30]

Summarizing, among Bantu (and similarly placed populations), calcium intake is much lower, and among women, the physiological drain of the element is far greater, compared with the situation among Whites. These handicaps signify that if level of calcium intake be critical in osteoporosis, then the disease in elderly Bantu should be almost invariable (at least in females) and occur often in a severe form.

Prevalence of Osteoporosis. Current textbooks on medicine in the tropics and semi-tropics scarcely mention osteoporosis.[31-33] However, studies have shown that the condition certainly occurs among local Bantu.[34-38] In Johannesburg, at Baragwanath Hospital (2,300 beds, and serving about 700,000 persons), according to Seftel,[37,38] at present there is an average of about fifty patients admitted to hospital annually with clinically severe osteoporosis. Among the sufferers, however, enquiry has revealed a number of remarkable features. (1) Three quarters or more of the patients are under 60 years, many being in the young middle age period. Only about a dozen are over 60 years. (2) Almost all patients are males. (3) Virtually all have severe abnormal iron deposition or siderosis (from habitually high iron intake[39,40]). (4) About a quarter have scurvy. The precise rôle of siderosis in promoting osteoporosis is not yet evaluated;[36,37] that of scurvy has been postulated.[34-37,41,42] At Lourenco Marques, Mozambique,

siderosis is rare and scurvy uncommon; enquiries at local hospitals indicate that osteoporosis, at least of the severe variety, is very unusual in Bantu patients. Presumably, therefore, the bulk of the osteoporosis seen in Johannesburg Bantu is a special phenomenon. At Cape Town, where siderosis is less common than in Johannesburg, Jackson[43] considers that the Bantu show little or no evidence of skeletal disease.

In the U.S.A., where about a fifth of the population are over 60 years, as stated previously, 4 million of the elderly are believed to have clinically severe osteoporosis;[1] the implication is that about one elderly person in ten is thus affected. In Johannesburg, there are at least 10,000 Bantu over 65 years. If clinically severe osteoporosis is equally prevalent in elderly Bantu and Whites, then several hundred Bantu should be suffering from the disease. If the calcium deficiency hypothesis is valid for these people, then many thousands of elderly Bantu in Johannesburg should be severely affected. It cannot be credited that this is so.

In addition to the information given, there are other grounds, admittedly indirect, for deeming that osteoporosis may be truly uncommon in these people. (1) Bhandarkar and Nordin[44] have reported that 20 per cent of the osteoporotics studied by them exhibit hypercalciurea. Urines from 400 Johannesburg Bantu "pensioners" (the most indigent of Bantu), 200 from each sex, have been examined for calcium/creatinine ratio. Ages ranged from 60 to 90 years, the mean being 67 years. Only 3 of the 400 subjects examined had a calcium/creatinine ratio exceeding 0.20 (the mean value was 0.065); i.e. only 3 subjects were hypercalciuric according to Nordin's classification. Hence, a high urinary excretion of calcium is very unusual in these people. Incidently, it may be of interest to add that since hypercalciuria is often associated with urolithiasis,[45-47] the low excretion of calcium in the urine of Bantu is consistent with the fact that kidney and bladder calculi occur very rarely in these people.[48] This A relatively low excretion of calcium, ~~in the urine~~, of course, does not

exclude the presence of osteoporosis. (2) While some osteoporotic patients have benefited from vitamin D therapy, the explanation is still a subject of controversy.[1,6,9,18,49] Be this as it may, vitamin D from radiation is more abundant in the tropics and semitropics compared with countries enjoying a temperate climate. In this respect, it is noteworthy that osteomalacia is virtually unknown in the Bantu. (3) Although calcium intake is low, balance experiments performed by us on Bantu prisoners, in agreement with observations undertaken on similar subjects elsewhere,[50,51] show the element to be well absorbed and retained, in spite of the possibly adverse influence of a somewhat lower protein intake,[52] and a higher phytic acid intake,[53] than in Whites. Presumably related to this efficient mechanism, we have found, in a comparison of mineral matter per unit volume of 5th thoracic vertebral bodies of Bantu and Whites, that the Bantu have higher mineral density.[54] In this connection, it may be noted that a number of studies have indicated that U.S.A. Negroes have greater bone density than Whites.[55,56] (4) Increasing importance is being attached to the rôle of activity in promoting calcification.[57,58] Undoubtedly, Bantu are more active than Whites, although outwardly the only really hard workers are mine-labourers and women working at the kraals and in the fields. At birth, the psychomotor activity of Bantu appears to be much greater than that of Whites;[59] furthermore, there is evidence that the motor fitness of children, and younger and older men, as assessed by the Harvard Step Test, far transcends that of corresponding White groups.[60,61] The bearing of this superiority, however, on the subject under discussion is not known.

From the information discussed, it would seem very doubtful whether osteoporosis is ubiquitous in old Bantu, as indeed it should be, if a low calcium intake is the primary aetiological factor in the disease.

It must be made clear, however, that no definitive osteoporosis

studies on hospital in-patients, out-patients, or random Bantu populations have yet been undertaken. It is possible that there may be a number of old people with fractured vertebrae who have no pain, or pain insufficient to cause them to seek medical relief, or that the condition is insufficiently looked for at hospital. The same uncertainty may well apply to a proportion of old people with mildly fractured femurs. It is also possible that the pain threshold of Bantu is higher than that of Whites, or, alternatively, that in their stoicism, backache may be regarded by Bantu as a normal accompaniment of old age. It is still conceivable, therefore, that osteoporosis is somewhat commoner in elderly Bantu than is suggested by hospital data.

Thus far, enquiry has been pursued specifically in relation to the situation regarding calcium intake and osteoporosis in a particular underprivileged Non-White population. The problem of whether osteoporosis is a calcium deficiency disease generally will now be enquired into in the orthodox manner, that is to say, by the same procedure that the classical deficiency diseases have been examined and established as such.

NUTRITIONAL DEFICIENCY AND OSTEOPOROSIS.

According to Yudkin,[62] there are three main diagnostic criteria of nutritional deficiency.

1. There must be evidence of deficient intake or utilization, primary or conditioned, of the nutrient.

2. The signs and symptoms must be specific for the particular deficiency.

3. The condition should be prevented or cured when the deficiency is made good.

1. Evidence of nutritional deficiency.

Pursuit along this avenue of enquiry is handicapped by the fact that the signs and symptoms of calcium deficiency in humans have

not been defined. Epidemiologically, relevant information bearing on calcium intake and osteoporosis is meagre.

2. Signs and symptoms.

Information on these aspects should be forthcoming from clinical or laboratory observations.

(a) Radiological appearance. While osteoporosis is characterized by rarefaction of bone, decreased bone density can arise from a variety of conditions, including osteomalacia, hyperparathyroidism, and thyrotoxicosis.[63] Some workers, such as Barnett and Nordin,[64] regard bioconcavity of vertebral bodies as characteristic and employable as an index of the frequency and severity of the disease. Caldwell,[65] however, in his investigation, found severe bioconcavity in 5 per cent of patients with normal vertebral bodies; but he also found the feature to be absent in 60 per cent of bodies found to be porotic. Vost,[66] too, from his studies has concluded that bioconcavity is not a reliable guide to the extent of osteoporosis. Thus, neither bone rarefaction nor bioconcavity of vertebral bodies are specific stigmata of osteoporosis.

(b) Biopsy and post-mortem studies of bone. (i) Histopathological examination of bone biopsy material (e.g. from the iliac crest) reveals that bone depletion does not occur uniformly in the same bone.[66-68] (ii) Collapse of vertebral bodies is not specific for osteoporosis. The situation is made more confused in that collapsed vertebral bodies are not usually contiguous.[68] In agreement with this observation, we have found normal mineral concentration in lumber vertebral bodies of Bantu adjacent to bodies with severe collapse and greatly reduced

mineral concentrations.[54] (iii) Caldwell,[65] in vertebral bodies from male and female having the same roentgenologic density, found that there was a lower concentration of calcium per unit volume in the bones of the females. Thus, in addition to the non-specificity of the roentgenological stigmata of osteoporosis, there is non-specificity stemming from the heterogeneity of bone, whether from biopsy or necropsy material, whether in relation to histopathological assessment or for mineral density determinations. The foregoing not only adds to the difficulty of pursuing this enquiry, but also adds to the difficulty of arriving at the precise prevalence of osteoporosis in different population groups.

(c) Retention of calcium by osteoporotic patients.

Many investigators,[1,6,8,14,15,17,69] from studies admittedly usually short-term and undertaken on few subjects, have reported a high retention of calcium by osteoporotic patients compared with "normal" subjects, when ingesting large amounts of the element. This finding, when combined with bone rarefaction noted on X-ray appearance, has led to the conclusion that such retentions reflect depleted calcium stores and hence provide a major clue of etiological importance. Three considerations, however, caution against the ready acceptance of this conclusion. (i) Excessive retention of a nutrient does not necessarily indicate previous need. Most adults can eat more food, consume more fat, and put on weight with consummate ease; yet the adult body seldom needs these additions. In the case of another mineral element, iron, studies on White adults have shown that high intakes cause the

retention of unneeded iron;[70,71] among adult Bantu, whose diet almost habitually is high in this element (largely adventitious, arising from the acid fermentation of cereal products in iron containers), concentrations of iron in liver and spleen may reach 5 and 10 per cent respectively. The high retention of calcium by osteoporotic patients, therefore, while suggestive, need not betoken previous need. (ii) The second objection concerns the ~~point~~ fact that the evidence that these large retentions actually do occur over very long periods is not unanimous. While some studies (cited above) support the belief, other studies, equally emphatically, support the contrary view. Thus, in one recent investigation it was found impossible to obtain prolonged positive calcium balances in ~~osteoporosis~~ osteoporotics with either high calcium intake, anabolic hormones, or sodium fluoride.[73] In another study, in which stools were marked with chromium sesquioxide, administration of calcium supplements failed to cause increased retention of the element.[74] The validity of the interpretations of long-term balances relating to calcium and ~~of~~ other nutrients has been challenged elsewhere.[75] Nordin[11] himself doubts whether the true positive balances are as great as the balance data indicate. Malm[76] regards as "monstrous" the suggestion that the large accretions of calcium demonstrated by some of the subjects in his long-term studies imply correspondingly large increases of new bone. Malm prefers to believe in long-term cycles of fluctuations of positive and negative calcium balances, a view previously put forward by German workers.[77] The precise situation regarding the retention of calcium from high intakes of the element

therefore remains uncertain. (iii) The third objection concerns the absence of evidence (apart from two recent studies[15,16]) that the high retentions claimed, even after long periods, improve roentgenologic bone density.

3. Prevention or remedy by increasing intake of appropriate nutrient.

The third criterion of nutritional deficiency is that the condition should be prevented or cured when the deficiency is made good. Urist[18] has written: "It has not been established that life long high calcium diet is any insurance against osteoporosis; it is possible that it may be detrimental in latter life". Our knowledge of the clinical response of osteoporosis to present therapeutic treatments is unsatisfactory. Backache itself, the main clinical feature, is a non-specific parameter; moreover, threshold of pain differs undoubtedly from individual to individual, and possibly between the sexes and races. Urist[19] has stated that "backache caused by fracture often subsides after three weeks of healing without any treatment". In Bantu with osteoporosis involving severe fractures to vertebral bodies, Grusin and co-workers,[34,35] also Seftel,[38] found that bed rest alone for 1 - 2 weeks, with no therapy, removes pain and renders ambulant a proportion of sufferers. Investigations bearing on the relief of pain afforded by therapeutic substances, when compared with placebos, have been insufficiently pursued. The symptomatic relief of pain provided by estrogens has been used by many observers as a criterion of the effectiveness of the therapy; yet the belief requires critical examination since Solomon et al.[78] showed the therapy largely to be a placebo phenomenon. Corresponding studies comparing calcium supplements with placebos have not been reported. Harrison,[79] referring to relief from back pain following therapy of calcium supplements or sex hormones, has stressed the uncertainty concerning how much of the relief is due to a placebo effect. It is urgently

imperative, therefore, by means of long-term studies on osteoporotics to elucidate the respective responses of pain to bed rest, placebos, supplements of calcium, and steroids (singly, and in combination), and other therapeutic measures. The claims bearing on reduced incidence of fractures and arrest of osteoporosis, following these various treatments, also require careful elucidation.

It will be apparent that this brief enquiry in relation to osteoporosis being primarily a calcium deficiency disease, has been inconclusive. Yet the examination has been made along the same lines that have demonstrated incontestibly that the classical deficiency diseases, also kwashiorkor and iron deficiency anaemia, are nutritional deficiency diseases.

EVIDENCE OF A RACIAL OR ETHNIC FACTOR IN OSTEOPOROSIS.

The commonness of osteoporosis in Whites, and its apparent uncommonness in U.S.A. Negroes, also in the Non-White population studied, raises the question of the existence of a racial or ethnic factor in the disease. Smith et al.[67] consider that this factor may well be important. In their series of 218 ambulatory women over 45 years, none was a Negro, although the patient source was a heterogeneous population. Evidence bearing on the greater bone density of Negroes and Bantu compared with Whites,[24,55,56] has already been referred to.

It is important to recognize that there are many situations in which factors promotive of pathology in one population do not apparently evoke the same deleterious response in others. According to our own investigations, scurvy should be common in prematurely weaned urban Bantu infants, yet the disease is extremely rare, and would seem in fact to be commoner in White infants.[80] Among sophisticated Bantu, we believe that myocardial infarction occurs far less frequently than would be predicted.[80,81] Among Bantu alcoholics, the fatty liver of cirrhosis is far less common than would be expected.[80] In the United States, perhaps

paradoxically, the much greater prevalence of hypertension and hypertensive heart disease in Negroes compared with Whites still awaits explanation.[82] Lowenstein[83] has recently stated (in regard of coronary heart disease) that factors "that may be harmful in one group may be harmless in another". This writer has put forward that there are definite limitations attached to the application of lessons learnt from underprivileged Non-White to White populations.[84] At present, therefore, it would be unwise to exclude the operation of a racial or ethnic factor in bone calcification. Malm[85] shares this view and considers that because underprivileged people, (such as Bantu), apparently do not evince the high prevalence of osteoporosis to be expected, this certainly does not disprove that level of calcium intake may be an important factor in the etiology of the condition as seen in western populations.

FUTURE RESEARCH.

What studies should be undertaken to elucidate the factors responsible for the causation of osteoporosis? The F.A.O. - W.H.O. Expert Group on Calcium Requirements[86] made numerous recommendations for future research. It is considered that perhaps the most rewarding avenues of approach may be as follows:-

1. The first need is to establish the prevalence of roentgenologic bone rarefaction due to osteoporosis in different population groups, employing methods and criteria which can be used in diverse countries, especially by workers in regions with limited resources. The methods, etc., could be laid down in a manner similar to those recommended internationally for the collection and grading of arterial tissue.[87] It would be highly desirable, moreover, for a representative proportion of roentgenograms (as well as <u>all</u> the relevant clinical,

pathological, and other information) to be made available to reference centres for critical comparative assessment, as is practiced in interracial studies on the grading of arterial tissue now being undertaken at New Orleans,[88] Boston,[89] and elsewhere.

2. Since evidence suggests that an ethnic or racial factor may be involved, measurement of physical density and other observations should be made on bones from different racial groups, and examined again preferably at reference centres.

3. The third urgent need concerns the careful long-term assessment of the clinical and other responses to calcium and other therapeutic substances and placebos.

Only by concerted means will it be possible to solve the "riddle" of osteoporosis,[79] and thus learn of the extent of the rôle of calcium intake in its pathogenesis.

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Studies in Human Mineral Metabolism

1. THE EFFECT OF BREAD RICH IN PHYTATE PHOSPHORUS ON THE METABOLISM OF CERTAIN MINERAL SALTS WITH SPECIAL REFERENCE TO CALCIUM

By A. R. P. WALKER, F. W. FOX and J. T. IRVING, *The South African National Nutrition Council, the South African Institute for Medical Research, Johannesburg, and the Department of Physiology, University of Cape Town*

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The discovery that phytic acid forms relatively insoluble salts with several of the common bases, that are of importance in our diet, has led to several investigations in which the availability of these bases has been determined with varying intakes of phytic acid. The conclusions drawn from such work have been somewhat contradictory: thus, whilst all observers are agreed that the addition of a considerable amount of phytate P is invariably followed by an immediate reduction in the amount of Ca retained, some investigators have suspected, and others are emphatic, that, given time, an adaptation to such a change can occur, and that eventually the body is able to adjust itself fairly satisfactorily to the new conditions.

Obviously laboratory investigations must eventually be reconciled with what happens in everyday life, and a consideration of those human diets which are rich in cereals and hence in phytic acid, yet poor in Ca, lends a considerable amount of support to the view that some such process of adaptation must in fact take place. Otherwise it is difficult to explain how the consumers avoid the disastrous consequences which would arise if part or the whole of this Ca were rendered unavailable.

For two reasons this issue is of particular importance to a country like South Africa. In the first place the large majority of the population, including most of the non-Europeans and not a few of the poorer Europeans, live on just such a diet as has been mentioned above. Secondly, in 1941, a compulsory Standard War Bread, made from 95 to 100 % extraction meal, was introduced and is still the only kind of bread allowed to be baked.

As a result of the work published by McCance & Widdowson (1942), the South African National Nutrition Council decided that it was imperative to study the problem under local conditions. For this purpose balance experiments, similar to those described by these workers, were initiated to observe the effects of breads made from high and low extraction meals upon mineral metabolism in adult male subjects.

EXPERIMENTAL

Plan of the experiments. The intake and excretion of Ca, Mg, total P, phytate P and Fe, were determined on four healthy adult European males, over periods ranging from 3 to 19 *consecutive* weeks.

The experimental periods were planned as follows: *A*, from 1 to 2 weeks on the usual everyday diet; *B*, from 4 to 9 weeks on a diet which contained 1 lb. of Standard War Bread (experimental diet no. 1); *C*, from 1 to 4 weeks in which the war bread was replaced by 1 lb. of white bread (70% extraction; experimental diet no. 2). For the first subject only the first two of these periods were observed, as this part of the experiment was of a preliminary nature carried out to gain acquaintance with the procedure.

The balance procedure and the analytical methods employed followed those described by McCance & Widdowson (1942), except in the following details: (i) Tap water was used throughout. (ii) Experience showed that the analytical procedure was facilitated by keeping the food samples separate for the following groups: milk, drinks, fatty foods, eggs, bread, and the remaining foodstuffs, i.e. soup, meat, vegetables, fruit, puddings and so forth. To obtain a thoroughly representative sample this last group was taken to dryness and finely ground. (iii) The total faeces for the week were also taken to dryness and finely ground before sampling.

Subjects. Three of the subjects were research biochemists and the fourth a reliable laboratory technician. During the investigation they lived in their homes and pursued their usual avocations. Health remained excellent in all cases throughout the investigation; no digestive or other disturbances were reported, and fluctuations in weight were insignificant. Some inconvenience was experienced in consuming the required amount of bread, but apart from the tedium inevitably associated with the daily weighing of all foods, etc., no difficulties were encountered.

RESULTS

Phytate-phosphorus content of meal and bread

Analysis of 12 samples of our meal showed that it contained an average of 205 mg. phytate P/100 g. as compared with 214 mg. found for the overseas 92% extraction product. In addition, when samples of bread obtained from bakeries throughout the country were analyzed, it was found that the average figure for 33 loaves was 50 mg. phytate P for 100 g. of fresh bread, as against 'about 100 mg.' found by McCance & Widdowson. Hence our meals were not only no richer in phytate P, but evidently a far greater destruction of this substance had occurred during the baking than in the case of the British 92% extraction loaf.

For the sake of brevity the terms 'brown' and 'white' breads are employed when referring to the 95–100% and the 70% extraction breads respectively.

Results of balance experiments

In view of the recent findings of Steggerda & Mitchell (1946*b*) that faecal Ca may not represent only unabsorbed Ca, attention has been focused solely upon the daily balance of the various elements.

Calcium metabolism

The results are given in Table 1.

A. *Period on the usual diet.* This period was included in order to evaluate the subject's nutritional state before the experimental diets were given. It will be seen that the subjects A.W., L.O. and L.G. were all in slight positive balance.

B. *Experimental diet no.* 1. The subjects were required to consume 1 lb. of Standard War Bread daily, but otherwise they were permitted to eat what they liked, except that the total Ca intake was regulated by adjusting the amount of milk and cheese consumed so as to comply with the requirements based on body weight (10 mg./kg. daily; see p. 458).

Subject F.F. As mentioned above, this study was of a preliminary nature. The subject immediately went into negative Ca balance, which however became less as the experiment proceeded. It was this fact, together with the gradual improvement in the amount of Ca retained, which made us realize the necessity for continuing our observations for prolonged periods. Accordingly it was decided to commence a more lengthy study, during which the degree of adjustment to each change in diet could be followed as quickly as analytical determinations of Ca would permit. In practice it was found possible to be not more than 1 week behind with these determinations. This enabled us to decide when a steady state had been reached, so that the next part of the investigation could be safely proceeded with.

Subject A.W. For no less than 4 weeks this subject remained in continuous negative balance (designated period B_1); this was followed by a further 5 weeks (designated period B_2) during which the balance was continuously positive, or almost positive. If McCance & Widdowson's (1942) suggested limits of significance of $\pm$ 25 mg./day are accepted, this subject may be regarded as having reached a state of equilibrium.

Subject L.O. This subject needed 5 weeks to adjust to the new diet (period B_1) and he then remained in equilibrium for the following 3 weeks (period B_2). It must, however, be mentioned that he experienced some difficulty in consuming the full 1 lb. of war bread daily, and hence his intake of other foods tended to suffer. In order to supply the daily requirement of Ca estimated on body weight, a small additional allowance of milk was therefore permitted after the 5th week.

Subject L.G. This subject proved of particular interest to us, since his Ca intake on his usual diet was found to be only just adequate for maintenance. With the experimental diet his Ca intake remained unchanged, and hence, unlike the other subjects, he only had to adjust to the increased ingestion of phytate P. It is presumably for this reason that he

Table 1. *Daily intake, excretion, and retention of calcium and magnesium, from the usual, brown-bread, and white-bread diets*

Period: Duration and sequence (days)	Designation	Diet consumed	(1) Calcium: Intake (mg.)	Urine (mg.)	Faeces (mg.)	Total excretion (mg.)	Balance (mg.)	(2) Magnesium: Intake (mg.)	Urine (mg.)	Faeces (mg.)	Total excretion (mg.)	Balance (mg.)
		Subject F.F. Weight 65 kg. Age 50 years										
3	*A*	Usual diet	—	225	914	1139	—	—	98	300	398	—
4	*B*	Experimental diet no. 1 including 1 lb. of standard war bread daily	535	192	504	696	−161	490	108	372	480	+ 10
7	*B*	,, ,, ,,	501	235	512	747	−246	480	89	395	484	− 4
7	*B*	,, ,, ,,	490	210	350	560	− 70	535	91	440	531	+ 4
4	*B*	,, ,, ,,	533	205	390	595	− 62	560	93	450	543	+ 17
		Average figures for period *B*	510	214	437	651	−141	514	94	415	509	+ 5
		Subject A.W. Weight 51 kg. Age 31 years										
(weeks)												
1	*A*	Usual diet	1160	246	848	1094	+ 66	495	80	405	485	+ 10
2	*A*	,,	1175	256	865	1121	+ 54	490	81	415	496	− 6
		Average figures for period *A*	1167	251	856	1107	+ 60	492	80	410	490	+ 2
3	B_1	Experimental diet no. 1 including 1 lb. of standard war bread daily	510	194	402	596	− 86	525	86	450	536	− 11
4	B_1	,, ,, ,,	512	203	387	590	− 78	550	79	620	699	−149
5	B_1	,, ,, ,,	524	220	373	593	− 69	575	126	570	696	−121
6	B_1	,, ,, ,,	501	269	297	566	− 65	575	133	545	678	−103
		Average figures for period B_1	512	221	365	586	− 74	556	106	546	652	− 96
7	B_2	Same as in period B_1	509	225	255	480	+ 29	500	59	430	489	+ 11
8	B_2	,, ,,	515	217	320	537	− 22	585	75	560	635	− 50
9	B_2	,, ,,	509	201	321	522	− 13	575	79	485	564	+ 11
10	B_2	,, ,,	561	219	295	514	+ 47	580	87	475	562	+ 18
11	B_2	,, ,,	488	196	257	453	+ 35	500	77	415	492	+ 8
		Average figures for period B_2	516	212	289	501	+ 15	547	75	473	548	− 1
12	C_1	Experimental diet no. 2*a* including milk, white rolls and potatoes daily	440	170	235	405	+ 35	310	76	225	301	+ 9
13	C_1	,, ,, ,,	486	145	272	417	+ 69	337	91	235	326	+ 11
14	C_1	,, ,, ,,	491	183	285	468	+ 23	300	75	210	285	+ 15
15	C_1	,, ,, ,,	499	170	260	430	+ 69	275	80	185	265	+ 10
		Average figures for period C_1	479	167	263	430	+ 49	305	80	214	294	+ 11
16	C_2	Experimental diet no. 2*b* including 1 lb. of white bread daily	512	245	235	480	+ 32	290	75	195	270	+ 20
17	C_2	,, ,, ,,	503	260	230	490	+ 13	285	80	195	275	+ 10
18	C_2	,, ,, ,,	471	200	225	425	+ 46	250	56	190	246	+ 4
19	C_2	,, ,, ,,	498	155	255	410	+ 88	245	36	195	231	+ 14
		Average figures for period C_2	496	215	236	451	+ 45	268	62	194	256	+ 12

		Subject L.O. Weight 64 kg. Age 28 years									
1	*A*	Usual diet	1090	139	936	1075	+ 15	512	146	360	506	+ 6
2	*A*	,,	927	132	780	912	+ 15	435	92	335	427	+ 8
		Average figures for period *A*	1008	135	858	993	+ 15	473	119	347	466	+ 7
3	B_1	Experimental diet no. 1 including 1 lb. of standard war bread daily	465	117	355	472	− 7	410	145	295	440	− 30
4	B_1	,, ,, ,,	485	123	375	498	− 13	440	190	322	512	− 72
5	B_1	,, ,, ,,	506	149	394	543	− 37	480	138	380	518	− 38
6	B_1	,, ,, ,,	504	155	367	522	− 18	508	130	430	560	− 52
7	B_1	,, ,, ,,	465	141	450	591	−126	550	101	510	611	− 61
		Average figures for period B_1	485	137	388	525	− 40	478	141	387	528	− 50
8	B_2	Same as in period B_1	620	133	480	613	+ 7	551	110	440	550	+ 1
9	B_2	,, ,,	630	97	520	617	+ 13	482	70	425	495	− 13
10	B_2	,, ,,	660	140	510	650	+ 10	566	120	428	548	+ 18
		Average figures for period B_2	636	123	503	626	+ 10	533	100	431	531	+ 2
11	*C*	Experimental diet no. 2 including 1 lb. of white bread daily	750	182	517	699	+ 51	318	111	202	313	+ 5
12	*C*	,, ,, ,,	720	170	535	705	+ 15	278	115	166	281	− 3
13	*C*	,, ,, ,,	695	110	495	605	+ 90	265	102	153	255	+ 10
		Average figures for period *C*	722	154	516	670	+ 52	287	109	174	283	+ 4
		Subject L.G. Weight 75 kg. Age 35 years									
1	*A*	Usual diet	763	193	537	730	+ 33	443	134	335	469	− 26
2	*B*	Experimental diet no. 1 including 1 lb. of standard war bread daily	740	269	550	819	− 79	790	137	584	721	+ 69
3	*B*	,, ,, ,,	719	220	504	724	− 5	677	172	528	700	− 23
4	*B*	,, ,, ,,	705	210	485	695	+ 10	735	175	518	693	+ 42
5	*B*	,, ,, ,,	880	233	595	828	+ 52	755	190	560	750	+ 5
		Average figures for period *B*	761	233	533	766	− 5	739	169	547	716	+ 23
6	*C*	Experimental diet no. 2 including 1 lb. of white bread daily	890	320	535	855	+ 35	465	185	270	455	+ 10

required only 3 weeks to reach equilibrium. After 2 weeks of positive Ca balance it was considered permissible to proceed with the next experimental diet.

C. *Experimental diet no.* 2. *Subject A.W.* Before passing on to the white-bread diet, this subject for a period of 4 weeks was given a diet in which the Ca supplied by the war bread was replaced mainly from milk. The supply of calories was maintained by means of white rolls and extra potatoes (period C_1). The amount of phytate P was thus very considerably reduced, although not as much as might be expected, since white rolls contain more of this substance than white bread made from the same flour. The Ca retention of the first balance period on this diet was the same as that of the last of the previous series. Thereafter the balances became more positive.

After this period of 4 weeks, the subject was placed on a diet in which the rolls and extra potatoes were replaced by 1 lb. white bread (period C_2). It will be seen that the retention of Ca was hardly affected. This period was continued for 4 weeks, and the consistency of the results showed that the subject was well adjusted to the change.

Subjects L.O. and L.G. changed over directly to the white-bread diet without the intervening period C_1. (It is unfortunate that, for reasons beyond our control, both L.O. and L.G. inadvertently consumed slightly more Ca than had been intended.) L.O. showed a slight improvement in Ca retention, while L.G. was virtually in equilibrium in the single balance period in which he was studied.

Magnesium metabolism

The intake of Mg, as will be seen from Table 1, even on the white-bread diet, was always ample for maintenance, i.e. it exceeded 250 mg. daily, the standard suggested by Duckworth & Warnock (1942).

McCance & Widdowson's (1942) subjects were in equilibrium throughout their experiments, but we found, on passing from the usual to the brown-bread diet, that two of our subjects began to lose more Mg than they ingested. As with Ca, however, Mg retention gradually improved. The urinary excretion of Mg was markedly increased during part of the brown-bread-diet period. During the white-bread period, the same total amount was retained as in the previous period, although the intake was only half of that on the brown-bread diet. The possible effect of variations in the Mg intake upon the utilization of Ca is referred to in a later section.

Total phosphorus metabolism

For the sake of brevity the metabolism data for total P and phytate P have been given in Tables 2 and 3 as averages for the different dietetic periods. This course was adopted because the weekly figures during those periods differed little from one another.

The metabolism of total P showed least disturbance of all the elements studied with the changes in diet. Although the amount consumed on the white-bread diet was less than that on the brown-bread diet, the retention rose somewhat. McCance & Widdowson (1942) found the same balance with either type of bread.

Table 2. *The daily intake, excretion, and retention of total phosphorus from the usual, brown-bread, and white-bread diets*

Period: Duration	Period: Designation	Diet consumed*	Intake (mg.)	Urine (mg.)	Faeces (mg.)	Total excretion (mg.)	Balance (mg.)
(days)	Subject F.F.*						
3	*A*	Usual diet	—	1520	650	2170	—
22	*B*	Brown-bread diet	885	1435	454	1889	− 4
(weeks)	Subject A.W.*						
2	*A*	Usual diet	1620	1020	542	1562	+ 58
4	B_1	Brown-bread diet	1415	870	529	1399	+ 16
5	B_2	Brown-bread diet	1380	862	483	1345	+ 35
4	C_1	Diet of milk, white rolls and potatoes	1107	760	291	1051	+ 56
4	C_2	White-bread diet	995	685	239	924	+ 71
	Subject L.O.*						
2	*A*	Usual diet	1495	740	752	1492	+ 3
5	B_1	Brown-bread diet	1559	1022	579	1601	− 42
3	B_2	Brown-bread diet	1716	1008	663	1671	+ 45
3	*C*	White-bread diet	1178	705	395	1100	+ 78
	Subject L.G.*						
1	*A*	Usual diet	1600	1000	560	1560	+ 40
4	*B*	Brown-bread diet	1825	1097	769	1866	− 41
1	*C*	White-bread diet	1540	930	500	1430	+110

* For fuller details see Table 1.

Table 3. *The daily intake, excretion, and retention of phytate phosphorus from usual, brown-bread, and white-bread diets*

Period					
Duration (days)	Designation	Diet consumed*	Intake (mg.)	Faeces (mg.)	Phytate hydrolyzed (%)
	Subject F.F.*				
3	*A*	Usual diet	—	135	—
22	*B*	Brown-bread diet	425	56	87
(weeks)	Subject A.W.*				
2	*A*	Usual diet	178	65	64
4	B_1	Brown-bread diet	289	33	88
5	B_2	Brown-bread diet	280	24	91
4	C_1	Diet of milk, white rolls and potatoes	84	26	69
4	C_2	White-bread diet	70	6	91
	Subject L.O.*				
2	*A*	Usual diet	142	53	63
5	B_1	Brown-bread diet	289	26	90
3	B_2	Brown-bread diet	345	38	89
3	*C*	White-bread diet	41	22	46
	Subject L.G.*				
1	*A*	Usual diet	105	60	43
4	*B*	Brown-bread diet	315	63	80
1	*C*	White-bread diet	90	50	44

* For fuller details see Table 1.

Table 4. *The daily intake, excretion, and retention of iron, from usual, brown-bread, and white-bread diets*

Period						
Duration (days)	Designation	Diet consumed*	Intake (mg.)	Urine (mg.)	Faeces (mg.)	Total excretion (mg.)	Balance (mg.)
	Subject F.F.*					
3	*A*	Usual diet	—	1·0	20·5	21·5	—
22	*B*	Brown-bread diet	26·1	0·4	24·6	25·0	+1·1
(weeks)	Subject A.W.*					
2	*A*	Usual diet	20·5	0·5	19·7	20·2	+0·3
4	B_1	Brown-bread diet	26·0	0·4	25·0	25·4	+0·6
5	B_2	Brown-bread diet	23·9	0·7	22·7	23·4	+0·5
4	C_1	Diet of milk, white rolls and potatoes	14·4	0·2	13·5	13·7	+0·7
4	C_2	White-bread diet	16·0	0·2	15·0	15·2	+0·8
	Subject L.O.*					
2	*A*	Usual diet	14·3	1·1	13·0	14·1	+0·2
5	B_1	Brown-bread diet	19·2	1·3	17·9	19·2	±0·0
3	B_2	Brown-bread diet	23·1	0·9	21·8	22·7	+0·4
3	*C*	White-bread diet	15·1	1·3	13·1	14·4	+0·7
	Subject L.G.*					
1	*A*	Usual diet	18·3	1·2	16·2	17·4	+0·9
4	*B*	Brown-bread diet	25·8	1·4	24·1	25·5	+0·3
1	*C*	White-bread diet	22·7	2·7	19·0	21·7	+1·0

* For fuller details see Table 1.

Phytate-phosphorus metabolism

When the Ca intake was high and that of phytate P comparatively low (i.e. on the usual diet), an average of 59% of the phytate P was hydrolyzed, whereas when the Ca intake was just adequate for maintenance and phytate-P intake high, an average of 84% was hydrolyzed. Judging by the conclusions reached by Harrison & Mellanby (1939), one might argue that in the absence of an abundance of Ca, the phytate P forms more readily hydrolyzable salts with bases such as Na and K. The condensed arrangement of the tables, however, masks the interesting fact that, after the change from the usual to the brown-bread diet, the amount of phytate P hydrolyzed reached its maximum extent *immediately*, without the incremental steps of adjustment found for Ca and Mg.

Iron metabolism

Following the suggestion made by McCance & Widdowson (1942), we carried out Fe balances for each subject, mainly because they afforded a simple means of checking the accuracy of the experimental procedure, more especially the marking off of the different faecal periods. The results (Table 4) show that the consumption of brown bread did not affect the amount of Fe retained. Such a conclusion would tend to support the work of several investigators who have found that the consumption of higher extraction breads had no deleterious effect upon the retention of this metal.

DISCUSSION

Environment

When a comparison is made between the experiments of McCance & Widdowson (1942) and our own, it should be pointed out that the present study extended over the different seasons. Owing to our climatic conditions, the subjects not only consumed food which had been fully irradiated by the sun, but were themselves continuously exposed to bright light at an altitude of approximately 6000 feet. There was thus this difference between the two studies, but, as shown by the very full review given by McCance & Widdowson, there is little evidence to suggest that the addition of vitamin D to the diet of healthy adults has any appreciable effect upon the absorption of Ca.

Calcium balances

At the outset we desire to draw attention to certain sources of error inherent in balance studies of this particular kind, which do not always appear to be sufficiently appreciated.

In recent years evidence has been accumulating that, when an individual who is habituated to one level of Ca intake is suddenly placed on a lower level, a period of adjustment is inevitable and may even be somewhat prolonged (Nicholls & Nimalasuriya, 1939; Cathcart, 1940; Steggerda & Mitchell, 1941; Kraut & Wecker, 1943). According to these workers the time taken to reach a steady state at the new level of Ca intake depends upon the magnitude of the difference between the two levels. It must also depend upon the extent to which the new supplies of Ca are available. Thus, if the reduction of the Ca intake is accompanied by an increase in the phytate-P intake, the negative balances following such changes cannot be interpreted as being solely due to the interfering effects of the phytate P.

Also, when passing from a high to a lower Ca intake it is necessary to insure that at least enough Ca is provided to satisfy the minimum requirements of the individual concerned. Otherwise the negative balances that will be observed are likely to be due to what may be termed an 'excretion momentum', in addition to any effects arising from a change in the availability of the supply. The difficult question of what constitutes a minimum daily requirement of Ca has recently been the subject of intensive study by Leitch (1937), Holmes (1945) and more especially Mitchell and his associates (Mitchell & Curzon, 1939; Steggerda & Mitchell, 1939, 1941, 1946*a*). These workers have reached substantial agreement with a figure of about 10 mg./kg. body weight, and we accordingly adopted this standard when planning our experiments.

Furthermore, in the reports given by some investigators the experimental periods are interrupted by days or weeks during which the food consumed is not specified. Unless the same level of Ca intake is maintained it seems inevitable that such interruptions will affect the subsequent observations. Lastly, there are other workers who employ such short experimental periods, and change the diets so frequently, that it is questionable whether the body has time to adjust itself to one diet before the next is taken. An extreme example of this is to be seen in the study reported by Wang, Liu, Chu, Yu, Chao & Hsu (1944), where, within the space of 38 days the diet was changed no less than twelve times.

The assimilation of calcium in the presence of phytic acid

Although our main experiments were carried out on only three subjects, the results obtained confirmed one another.

It is not easy to compare our findings with those reported by other observers because of the comparatively short experimental periods usually employed by them. Thus, whilst the experiments reported by McCance & Widdowson (1942) lasted intermittently over 9 months, the actual periods of continuous observation were usually 3–4 weeks. These workers were emphatic that there was no indication of any adaptation occurring. Similarly, the experimental periods employed by Krebs & Mellanby (1943) lasted for 4 weeks; but it is worth noting that before the experiments on the 85% extraction bread terminated, one of their six volunteers (no. 3) was already showing improvement in the retention of Ca and finally reached equilibrium. In their recent experiments with children, Hoff-Jørgensen, Andersen & Nielsen (1946) suspected that the retention of Ca was gradually improving with time. (We presume, although this is not stated, that the same diet, rich in phytic acid, was continued during the short intervals that occurred between their 5-day periods.) Indeed, had we discontinued our observations after 3–4 weeks on the high-extraction bread diet, our findings would have been

very similar to those obtained by these three groups of investigators.

Combining our own evidence with that already available, we suggest the following: subjects passing abruptly from their usual diet to one containing less Ca and much more phytate P show an immediate negative Ca balance. As the body becomes accustomed to such a diet, the retention of Ca improves, so that, *given time*, equilibrium again occurs and the losses of Ca are slowly made good. The period of adjustment is shorter, and the loss of Ca is less, if the disparity between the usual Ca intake and that of the experimental diet is small.

Evidence available from studies made on individuals habituated to diets high in phytate phosphorus and low in calcium.

There is, however, another method of approach which throws valuable light on the whole problem. Instead of placing a few selected individuals on prescribed diets and then observing how they adjust themselves to the new conditions over shorter or longer periods (which for obvious practical reasons can never be really very prolonged relative to the life span), it ought to be possible to gain more reliable information by studying people who, through force of circumstances, are compelled to subsist for long periods on diets which are very rich in phytate P and very low in Ca. Some of the few available Ca balance studies that are on record for such people have been assembled in Table 5.

Although we have deliberately selected examples where the Ca balances were positive, it may be stated that this obtained in all the cases reported by Nicholls & Nimalasuriya (1939); in two out of the five cases reported by Henderson & Kelly (1929–30) for boys on prison diet; in two out of four adult cases on the same type of diet (Kelly & Henderson, 1929–30); and in two out of the three subjects studied by Basu, Basak, & Sircar (1939). This must presumably indicate that such positive balances occur fairly frequently. Even the survival of these individuals on such diets is remarkable. That they are somewhat shorter and lighter than well nourished Europeans is admitted, but with a diet lacking in so many other respects it is hardly fair to attribute this solely to a lack of available Ca. As far as our rural South African Bantu are concerned there is not much evidence of poor skeletal calcification, whilst the teeth are often well formed and sometimes remarkably free from caries. Thus in a recent careful dental survey carried out on some 1000 Bechuanaland children, whose diet consists mainly of Kaffir corn, no less than 70% were found to be free from all signs of caries. Equally striking results have been reported by Wilson & Widdowson (1942) for Indian children.

It must be admitted that such observations cannot easily be reconciled with orthodox opinions; however, we do not consider it satisfactory to dispose of them as being due to racial differences, but think rather that they reflect an adaptation which any human being may be capable of making under similar circumstances. That somewhat similar adaptation can be achieved by Europeans is suggested by the experience of the French people during the occupation. They consumed a diet extremely low in Ca and including high-extraction bread (Paris

Table 5. *Examples of positive calcium balances observed with non-Europeans of different races when consuming their typical cereal diets, rich in phytate phosphorus and low in calcium*

Diet and authority	Sex and age (yr.)	Experimental period (days)	Intake (mg./day)	Urine (mg./day)	Faeces (mg./day)	Total excretion (mg./day)	Balance (mg./day)
(1) Nicholls & Nimalasuriya (1939). Sinhgalese children consuming usual diet of cereals, legumes, roots and vegetables	*M* 4	3	205	25	55	80	+125
	M 4	3	183	24	96	120	+ 63
	F 7	3	245	29	135	164	+ 81
	M 7	3	70	4	15	19	+ 51
	M 7	3	223	7	47	54	+169
	M 7	3	220	5	45	50	+170
(2) Henderson & Kelly (1929–30). Bantu boys consuming long term prison diet including 1·5 lb. maize, beans, potatoes, fat and meat. Average of two 4-day periods taken during a 21-day study	*M* 16	8	300	23	271	294	+ 6
	M 16	8	300	19	242	261	+ 39
(3) Kelly & Henderson (1929–30). Bantu adults consuming diet almost the same as in (2). Average of a 4-day period taken once during a 42-day study. Prison diets (2) and (3) both resembled diets commonly consumed	*M*	4	300	23	151	174	+126
	M	4	300	10	172	182	+118
(4) Basu *et al.* (1939). Indian adults. Diet (*a*) included 400 g. rice; average of 6-day period. Diet (*b*) included 600 g. whole wheat: average of 12 consecutive days	(*a*) *M*	6	280	70	162	232	+ 48
	(*b*) *M*	12	310	19	167	186	+124

letter, 1942), but it is claimed that the decalcification which might have been expected did not take place (Paris letter, 1946).

It is possible that some similar process of adaptation had occurred, though to a lesser extent, in our subjects, since for several years the inhabitants of South Africa have been restricted solely to the use of high extraction bread, and hence some degree of habituation to it may have occurred. This capacity for adjustment may well have been lacking in the subjects studied by McCance & Widdowson (1942).

The mechanism of adaptation to diets with a high phytic acid content

This adaptation can be explained in two ways: one based on our knowledge of the chemical changes which phytates may undergo in the intestine, the other on the body's known ability to adapt itself to a lower intake of Ca.

(*a*) *The digestion of phytate phosphorus.* Most workers seem to agree that phytate P and Ca combine to form an insoluble salt in the intestine. Thus Harrison & Mellanby (1939) from their work on puppies remark: 'It is not possible to say whether such actual precipitation occurs under the conditions present in the gut, but it seems not unlikely.' McCance (1946), discussing the position as far as humans are concerned, concludes that phytic acid 'precipitates Ca in the intestine and by so doing prevents its absorption'. Assuming that the pH values in the intestinal tract of man resemble those observed in the pig, Møllgaard, Lorenzen, Hansen & Christensen (1946) conclude that 'phytic acid may precipitate Ca even in the first part of the small intestine thus causing a serious fall in its absorption'. Hence the consensus of opinion is definitely that the precipitation of Ca by phytic acid occurs, and the fact must therefore be accounted for that much of this Ca is eventually absorbed.

There is general agreement that some degree of hydrolysis of phytate P occurs in the digestive tract. This has been demonstrated for pigs, rats, dogs and hens. Similar results for man have been reported by McCance & Widdowson (1935), Wang *et al.* (1944), Cruickshank, Duckworth, Kosterlitz & Warnock (1945), and recently for babies and children by Hoff-Jørgensen, Andersen, Begtrup & Nielsen (1946) and Hoff-Jørgensen, Andersen & Nielsen (1946).

As far as animals are concerned, the extent to which hydrolysis occurs appears to depend on the level of the Ca intake, e.g. for rats, hens and dogs it has been found that the lower the Ca intake the greater the amount of phytate P hydrolyzed. Likewise for man Cruickshank *et al.* (1945), in a study in which the cereal employed was oatmeal, found that the amount of phytate P hydrolyzed was inversely proportional to the Ca intake. Similar results are reported in the present paper.

At present there are two views as to how this hydrolysis is brought about in man. Some maintain that it is due to the action of the intestinal flora in the digestive tract, whilst Møllgaard *et al.* (1946) insist that hydrolysis can only occur when the diet contains a specific enzyme, which they regard as being normally destroyed when food is cooked.

Both in the case of animals and man there seems to be no difference of opinion that at least a proportion of the P liberated by hydrolysis is absorbed. The question at issue is whether hydrolysis occurs at such a level as will also permit of the liberated Ca being absorbed.

It has been shown that under certain circumstances this does take place in the case of pigs, rats, hens and dogs, and it is of interest to note that Hoff-Jørgensen, Andersen, Begtrup & Nielsen (1946) conclude from their experiments on children 'that a small part of the Ca which was precipitated as Ca phytate was absorbed'. Similarly, Wilson & Widdowson (1942) reviewing their Indian observations, where they were dealing with diets which contained a great deal more phytic acid P than was sufficient to precipitate all the Ca present, came to the same conclusion.

A further interesting point arises from a consideration of the part Mg may play in this connexion. It is more than likely that the phytate P precipitates in the intestinal tract a compound which is not solely the Ca salt, as seems to be assumed by Hoff-Jørgensen (1946), Hoff-Jørgensen, Andersen, Begtrup & Nielsen (1946) and Hoff-Jørgensen, Andersen & Nielsen (1946). Both Harrison & Mellanby (1939) and McCance & Widdowson (1942) have shown that when precipitation occurs *in vitro* in the presence of both bases, a mixed phytate is formed containing approximately equal equivalents of Ca and Mg. The latter workers, who attempted to simulate the conditions which occur in the intestinal tract in regard to pH value, are of the opinion that a precipitate of this nature is likely to be formed. Obviously this is an important point, for it would decide the amount of Ca made less available by a given amount of phytate P. Our own results tend to support the proposition that phytic acid reacted with Mg as well as with Ca.

(*b*) *The ability of the body to adapt itself to a lowered calcium intake.* Irrespective of the composition of the diet, it is now well known that the body can adapt itself to a Ca intake often well below 10 mg./kg. body weight daily. This has been stressed by Nicholls & Nimalasuriya (1939), Owen, Irving & Lyall (1940), Steggerda & Mitchell (1941, 1946*a*) and Kraut & Wecker (1943). This adaptation, in the present experiments, was not due only to increased hydrolysis of phytate, since the increased hydrolysis took place immediately the brown-bread regime was instituted, whereas the adaptation was gradual.

The ability of the body in this respect has been well summarized by Steggerda & Mitchell (1941) as follows: 'It appears that in the presence of an inadequate supply of any nutrient, including Ca, the body can adjust itself to the situation, either by a more economical use of what little is available, or by a lowering of its own requirements, so that eventually it comes into equilibrium with the limited food supply.' These writers (Steggerda & Mitchell, 1946*a*) consider that no harm can come from such an adaptation, provided the Ca intake is 10 mg./kg. body weight daily.

This work was originally undertaken to find out if the results of McCance & Widdowson (1942) applied in South Africa. It is evident that our results confirm those of these workers in so far as we have shown that a high-brown-bread regime renders a certain amount of the dietary Ca less available. However, further evidence shows beyond doubt that the body can adjust to this lessened availability, and that the consumption of such a diet over long periods has no deleterious effect upon Ca metabolism.

SUMMARY

1. The metabolism of calcium, magnesium, phosphorus, phytate phosphorus, and iron has been followed in three healthy adult European males for periods lasting from 7 to 19 *consecutive* weeks. During this time the subjects consumed (*a*) their usual diet, (*b*) a diet including 1 lb. of bread made from 95 to 100% extraction meal, and (*c*) a diet including 1 lb. of bread made from 70% extraction meal. During dietary periods (*b*) and (*c*) the daily calcium intake was restricted to a level of approximately 10 mg./kg. of the subject's body weight.

2. When the subjects passed abruptly from their usual diet to one containing much more phytate phosphorus and, in two cases, less calcium, they showed an immediate negative calcium balance.

3. As they became accustomed to such a change, the retention of calcium improved, so that, *given time*, equilibrium was again reached and the losses of calcium were slowly made good.

4. The period of adjustment was shorter, and the loss of calcium was less, if the disparity between the usual calcium intake and that from the experimental diet was small.

5. The lower the calcium content of the diet, the greater was the amount of phytate phosphorus hydrolyzed.

6. The results are tentatively explained as being due to hydrolysis of the calcium and magnesium phytate at such a level in the digestive tract as to permit of the calcium being subsequently absorbed, and to a gradual adaptation of the body to a lowered intake of available calcium.

7. In two of the subjects, the retention of magnesium was at first lowered by the diet containing more phytate phosphorus. It was considered that this might be due to the precipitation of magnesium by the phytic acid. Later, while the subjects were still on this regime, magnesium retention improved, and changed but slightly when the phytate phosphorus of the diet was lowered.

8. The retention of total phosphorus was at first lowered in two of the subjects by the addition of phytate phosphorus to the diet, but subsequently improved. It improved still further in all subjects when the phytate phosphorus of the diet was reduced.

9. The retention of iron was virtually the same with high and low phytate-phosphorus diets.

10. Cereal diets rich in phytate phosphorus and low in calcium are commonly consumed in various parts of the world; consideration of what must occur under these conditions, together with an examination of the small amount of relevant experimental evidence available, lends a considerable amount of support to the conclusions reached in this paper.

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CEREALS, PHYTIC ACID, AND CALCIFICATION

A. R. P. WALKER
M.Sc. Brist., Ph.D. Cape Town

MEMBER OF NUTRITION UNIT OF COUNCIL FOR SCIENTIFIC AND INDUSTRIAL RESEARCH, SOUTH AFRICAN INSTITUTE FOR MEDICAL RESEARCH, JOHANNESBURG

CEREALS are so important to human nutrition that any nutritional drawback attached to their consumption is a matter of more than academic interest. Within the last few decades it has been shown that cereals and certain cereal products contain a substance, recently identified as phytic acid, which has an anticalcifying action in dogs. Briefly, the belief is that, under certain conditions, this acid precipitates dietary calcium in the intestinal tract, and, by reducing the amount of calcium available for absorption, restricts growth and even causes rickets. This anticalcifying effect, so readily demonstrable in dogs, has been accepted widely as obtaining in man (*British Medical Journal* 1943, *Medical Journal of Australia* 1948, Hawk et al. 1949, Shafar 1949, Fearon 1948, Carter and Thompson 1949). One practical result has been that in Great Britain, during the war and thereafter, calcium carbonate has been added to the lightly milled bread flour to compensate for the deleterious effect of its relatively high content of phytic acid. In this paper experimental and field evidence on the subject is discussed, and an attempt is made to determine whether the anticalcifying activity of phytic acid is of practical importance in human nutrition.

Experimental Evidence

Using puppies, Mellanby (1921, 1925) demonstrated that cereals could be graded in their anticalcifying activity; he found that more severe rickets developed when the diet consisted mainly of oatmeal, maize, or whole-wheat flour, than when equal amounts of either white flour or rice was substituted for these. From later experiments, also undertaken with puppies, Harrison and Mellanby (1939) suggested that this rickets-producing property is normally due to the action of the cereal phytic acid in inhibiting the absorption of calcium from the alimentary canal; and that the property is only likely to operate in diets which are on, or below, the borderline of minimum requirements of calcium and vitamin D.

As regards man, several workers have shown that, when healthy adults are given a low-calcium diet accompanied by a high intake of phytic acid derived from whole grain or lightly milled wheaten bread, negative calcium balances occur (McCance and Widdowson 1942a and b, Krebs and Mellanby 1943, Walker et al. 1946, 1948, McCance and Walsham 1948). This phenomenon is also seen, under similar experimental conditions, when the phytic acid is derived from oatmeal (Cruickshank et al. 1945, McCance and Glaser 1948). Further, when two children, ingesting throughout, however, an adequate amount of calcium, were placed on diets at first low and later high in phytic acid derived mainly from rye bread, negative calcium balances also resulted (Hoff-Jørgensen et al. 1946). From these studies the conclusion has been reached that in man, under certain conditions, phytic acid has a disturbing effect on the retention of calcium.

Before attaching undue practical importance to this conclusion, however, other experimental observations should be taken into consideration.

(1) Calcium forms with phytic acid a salt which is insoluble in an aqueous medium at the pH value of the intestinal tract; but, even under relatively simple in-vitro conditions, complete precipitation does not take place when certain additional substances are present. At this pH value McCance and Widdowson (1942a) allowed the same equivalents of calcium, magnesium, and phytic acid to react as are present in a brown-bread dietary containing relatively little calcium but much phytic acid; although the amount of phytic acid present was sufficient to precipitate *all* the calcium, no less than about 30% of this element remained unprecipitated. I have repeated this type of experiment (Walker 1951), only using the corresponding amounts of these three components present in a South African Bantu diet, composed mainly of whole or lightly milled maize and beans—a diet also low in calcium and high in phytic acid. I found that much the same proportion of calcium was left in solution. Thus, part of the calcium was retained in solution owing to the presence of magnesium. Other substances present in the intestinal tract have a similar effect. It has been reported that calcium phytate is slightly soluble in an aqueous solution of certain amino-acids (Lehmann and Pollak 1942) and certain hydroxy acids, such as phosphoric acid (Møllgaard et al. 1946). Little is known of the effect of bile salts, intestinal secretions, &c., on the solubility of calcium phytate. Hence, because of the complex influence of the many different substances present in the human intestine, it is considered that, even when the diet contains far more phytic acid than is required to precipitate all the calcium ingested, the extent of the precipitation is uncertain.

(2) McCance and Widdowson (1935) found that, when four adults ingested a large amount of phytic acid derived from brown bread, 36–63% of the acid appeared unchanged in the fæces; the intakes of calcium were not stated. But in dietary conditions of low calcium and high phytic-acid intakes, that are encountered in practical nutrition, little or sometimes no phytic acid appears in the fæces. This has been observed with a diet containing a large amount of oatmeal (Cruickshank et al. 1945), with a diet which included about a pound of whole-grain bread a day (Walker et al. 1948), and with the Bantu diet, which contains a large amount of maize and beans (Walker 1951). Under such dietary conditions the presence of only small amounts of phytic acid in the fæces increases the uncertainty over the extent to which this acid precipitates calcium in the intestinal tract.

(3) There is a considerable amount of evidence that, when the calcium intake is reduced, adjustment is not immediately achieved but takes an appreciable time (Steggerda and Mitchell 1939, Nicholls and Nimalasuriya 1939, Cathcart 1940, Kraut and Wecker 1943, 1948, Walker et al. 1948). This raises two issues:

(*a*) In most of the studies referred to above, the everyday diet of the subjects was altered to one not only of increased phytic-acid intake but also of reduced calcium intake, the latter being usually less than 10 mg. per kg. of body-weight. Hence the negative balances which resulted were due to two causes—increased phytic-acid intake and decreased calcium intake. To consider them to be *wholly* due to the former cause is erroneous.

(*b*) Since adjustment takes time, the question arises: were the periods of observation in the above studies long enough to allow for such capacity as the body possesses in this respect to operate? McCance and Widdowson (1942a) reported that no improvement in calcium retention occurred among their subjects during 28-day periods. Of the subjects of Krebs and Mellanby (1943), observed for the same periods, one out of the six ultimately came into equilibrium. Hoff-Jørgensen et al. (1946), who used 5-day interrupted periods extending over 21 days, found some evidence to suggest that, had their two children been observed for a longer time, their absorption of calcium might have gradually increased. In the investigation of Walker et al. (1948), however, balance observations were made over longer periods, from 4 to 9 consecutive weeks; the calcium intake was maintained at about 10 mg. per kg. of body-weight; with the three subjects examined the negative balances after a time were reduced, equilibrium was reached, and positive balances began to occur. Hence the disturbing effect of phytic acid may not be permanent.

(4) Should the disturbing effect of phytic acid on the retention of calcium be permanent, slow decalcification of the bones and tissues *must* occur. No dietary experiments, however, have been continued long enough to check radiographically whether a long-term withdrawal of calcium takes place or not. An additional handicap

is that there is little knowledge as to how much calcium must be yielded up by the body before the loss can be detected by such methods.

(5) No long-term balance observations have been undertaken on children or pregnant and lactating women, who might be expected to be especially vulnerable to interference of calcium retention by phytic acid.

(6) Finally, all studies in calcium retention seem to have their importance limited by the observation of McCance and Widdowson (1943) that there are seasonal variations in the capacity to absorb calcium ; and by the observation of Kraut and Wecker (1948) that calcium retention is subject to a cyclical variation, during which time, within certain limits, the level of intake of calcium seems to be almost irrelevant.

SUMMARY

Under certain experimental conditions an increase in the intake of phytic acid by man has a disturbing effect on the retention of calcium : this phenomenon has been observed by balance experiment only ; it has not been confirmed radiographically. However, there is limited balance-experiment evidence available which suggests that the disturbing effect may not be permanent, but that the body, given time, and within limits, can adjust itself successfully to such a dietetic situation. Various uncertainties involved in the experimental evidence indicate that considerable caution is required in interpreting such evidence in terms of practical nutrition.

Field Evidence

The importance which has been attached to the anti-calcifying action of cereal phytic acid in man may be gauged from the following quotations. Mellanby (1925) stated : " Apart from extreme malnutrition, it would appear not improbable that in this country, where the average diet is deficient in or contains a borderline quantity of antirachitic vitamin and calcium, and where sunshine is negligible, the ingestion of oatmeal during pregnancy and lactation of women, and in growing children, does much harm " ; in 1937 he repeated this warning. Later, in 1944, he wrote that the problem of phytic acid " concerns what in the past certainly has been, and in my view possibly still is, the most prominent problem of malnutrition affecting people in Great Britain."

In Great Britain medical opinion seems to have been uncritical of the belief that the phytic acid of cereals and certain cereal products is rachitogenic to man. Bacharach (1945), however, doubted whether oatmeal per se would produce rickets in man. Yudkin (1949) has expressed the view that there is a growing feeling among nutritionists that the deleterious effect of phytate

in breads of high extraction has been over-emphasised. In America early authoritative opinion was unconvinced (*Journal of the American Medical Association* 1927). Hess (1930) paid only passing reference to it in his book on *Rickets, including Osteomalacia and Tetany*. The Council on Foods (1937) of the American Medical Association concluded that there was no good evidence for the existence of an anticalcifying factor in cereals, a view also maintained by McCollum et al. (1939) and inclined to by Shohl (1939). In Australia, Stanton Hicks (1949), commenting on recent studies by McCance and Walsham (1948), observed that only eighty years ago all Europeans consumed whole-meal flour, and that a number still do; he thought it unreasonable to assume that our ancestors suffered from an adverse calcium balance, and that tetany was common among them; and he concluded that history carries more weight than does laboratory experimentation with a few human beings for a short time.

EVIDENCE OF EARLY CLINICIANS

One of the best known of the early clinicians who wrote on rickets was Cheadle (1902). To give proper weight to his testimony it must be stated that he knew that rickets was common in cloudy regions but almost disappeared in the tropics; that light, especially full sunlight, was as important to the cure as to the prevention of rickets; that the removal of fat from milk favoured its development; and that cod-liver oil was effective as a cure. He observed that the disease was almost unknown among sucklings, but was especially common in "children fed almost entirely upon farinaceous preparations—oatmeal, cornflour, bread, and patent foods with little or no milk." Now, oatmeal contains a large amount of phytic acid; on the other hand, white bread (which was the staple by 1890) contains little more than a trace of phytic acid. If this acid is rachitogenic to man, it should have been observed that a regimen including a large amount of oatmeal was far more rachitogenic than one including an equivalent amount of white bread. In Jenner's time rickets was the most fatal of diseases affecting young children (Aitken 1870); in Cheadle's time (1902) it was also very common. Why, then, did able clinical observers fail to draw attention to an obvious difference in rachitic property between these two foodstuffs? Why also, even up to now, has this difference not been reported? This lack of clinical evidence raises doubts about the critical importance assigned to phytic acid in the ætiology of rickets in man.

SCOTTISH EVIDENCE

Since oatmeal is considered to be the most anti-calcifying of cereals, the past experience of the Scots

is very relevant, not only because of their traditional diet, which contained a very large amount of oatmeal, but also because of the relative scarcity of sunshine in Scotland. Mellanby (1925), however, anticipated the challenge. "If oatmeal is so detrimental to bone formation, how is it that fine races of men have been reared on diets of which this cereal forms a large part?" In answer he stated that, if the conclusions from the puppy experiments applied to man, "it is highly probable that the diet of these people also included much of foods rich in antirachitic vitamin, as, for example, milk, eggs, and fish of the fatty variety." Mellanby (1944) referred to the Scots overcoming the phytic-acid problem by taking milk freely with their porridge.

It is important to have an approximate idea of the amount of calcium theoretically required to nullify the anticalcifying property of 1 lb. of oatmeal consumed as porridge. This amount (which supplies about 1800 calories) contains as much as 1350 mg. of phytic-acid phosphorus (Mellanby 1944). If the calcium-magnesium salt of the acid is precipitated in the intestinal tract, the above amount of acid can precipitate about 800 mg. of calcium—i.e., the amount contained in about 1·2 pints of milk. Should the pentacalcium salt (Hoff-Jørgensen 1946) be formed, about 1450 mg. of calcium can be precipitated—i.e., the amount contained in just over 2 pints of milk.

Although little historical inquiry has been pursued in this matter, there is evidence that in the near past the diet of the rural Scottish people, who were reported to be "big-boned and well-developed" (Watson 1907) and to have good teeth (Haddon 1903), was much as Mellanby conjectured (Coirce 1906, Smith 1941); and that rickets, at least in the Highland child, was uncommon (Edie and Simpson 1911). In the Lowlands, from 1854 to at least 1900, even the usual prison diet included two pints of milk with the 1 lb. or so of oatmeal consumed daily (Dunlop 1899). But what of the earlier period when dietetic conditions were less favourable? In the Lowlands, in the early 1700s, according to Grieg (1946) and Kitchin and Passmore (1949), the food of the people included large amounts of oats and barley; of vegetables there was kale; and dried peas, beans, and lentils, rich sources of phytic acid, were used extensively. Little cow's milk was available, and in late winter it was almost totally absent. Such a diet was rich in phytic acid, probably low in calcium, and almost devoid of vitamin D. Should not rickets have been widespread? Findlay (1915), who read widely in his investigation of the causation of rickets, does not mention that it was so. I can find no relevant information either way. Even taking into account that fish was available at the coast and near the rivers, that in winter a certain amount of milk was

obtained from ewes and goats, and that a high consumption of kale would afford a relatively large contribution of calcium, surely, should the phytic acid hypothesis be valid in man, rickets would still be expected to be of frequent occurrence, for there was great poverty in the land. At a time, therefore, when the Scottish national diet contained a large amount of phytic acid and probably little calcium and vitamin D, it has not been possible to find any evidence that rickets was very common.

EVIDENCE FROM TROPICAL AND SEMITROPICAL REGIONS

The diet consumed in tropical and semitropical countries is often high in phytic acid and low in calcium ; moreover it often contains only a small amount of vitamin D. At first sight conditions for calcification seem to be very unfavourable. Actually, among the inhabitants who are well exposed to sunlight, rickets is reported to be rare ; corroborative evidence has been reported from East Africa (Moore 1940, Trowell 1948), Southern Africa (Gelfand 1944, Kark and le Riche 1944), India (Hutchison 1922, Wilson and Widdowson 1942), and China (Jefferys and Maxwell 1910, Wyatt 1930). Hence, where there is an abundance of vitamin D derived from radiation, a high intake of phytic acid, even in the presence of a low intake of calcium, seems to be unimportant in so far as rickets is concerned.

EVIDENCE FROM EIRE

So far, the evidence has concerned subjects habituated to a diet high in phytic acid. But an important point is what happens when the intakes of calcium and vitamin D are already low, and the ingestion of phytic acid is suddenly increased. Is it possible for the reduced absorption of calcium, that is stated to occur, to bring on an increase in the incidence of rickets ? In Eire this dietetic situation arose when war-time conditions caused the staple bread to be made from almost whole-grain flour, and an increase in the annual incidence of rickets did, in fact, take place. This happening is the main field evidence that has been cited in support of the phytic-acid hypothesis (McCance and Widdowson 1944, 1949, Kent-Jones 1946, Kent-Jones and Amos 1947).

Several considerations, however, preclude us from accepting this phenomenon as one of simple cause and effect.

(1) The fact that there was no control experiment is a disadvantage. This drawback has already been pointed out by Davidson (1946).

(2) In Dublin, among babies aged three to six months, who were affected little or not at all by changes in the composition of the bread, the annual incidence of rickets

was subject to even greater fluctuations than were observed in older babies (Walsh et al. 1946).

(3) There was a time-lag between the bread changes and the alterations in the incidence of rickets. The almost whole-grain bread was introduced in the spring of 1941, but the incidence of rickets only became particularly increased in Dublin in the spring of 1943 and in Cork in late 1942. The 82½% extraction bread, with its far smaller content of phytic acid, was introduced at the end of 1943; yet both in Dublin and in Cork, the incidence of rickets was higher in 1944 than in the previous year (Saunders 1944, Walsh et al. 1946).

(4) In the fifth and final report of the Dublin doctors (Walsh et al. 1946) it is clear that few conclusions can be reached about the extent to which the incidence of rickets was affected by (a) the extraction-rate of the flour, (b) the intake of milk, and (c) the intake of vitamin D.

Though the increase in incidence may have been influenced by the change in the composition of the staple bread, it is certain that other factors also operated. Saunders (1944), for example, considers the increase to have been largely due to the greater scarcity of foods and concentrates containing vitamin D. Whatever factors were responsible, the phenomenon can hardly be used as unequivocal evidence in support of the phytic-acid hypothesis.

Growth

Up to now the anticalcifying effect of phytic acid has been examined from the point of view of its possible rôle in the ætiology of rickets. The extent to which this effect may restrict growth will now be discussed.

Nicholls and Nimalasuriya (1939) have noted that the Sinhalese children appear normal, and their bones resemble those of Europeans in structure and composition, yet their intake of calcium is only 200–400 mg. a day; in addition, a fair amount of phytic acid derived from pulses, &c., is ingested daily. McCance and Widdowson (1942a) have drawn attention to the low stature of these children, and maintain that their height is less than that to which they would grow if their calcium intake and general nutrition were improved. More recently, these authors (1949) have stated that "no-one will deny that most adults can maintain health on diets which contain very little calcium and much phytic acid, or that children can absorb enough calcium to grow on such diets, but it is less certain that they grow at an optimum rate." The belief that, with other nutrients, a high intake of calcium is required for the attainment of height is common; nevertheless it is surprising how meagre is the evidence in its favour. Of importance in this issue are the experiments of Aykroyd and Krishnan (1938) made in India; they found that, when 56 nursery-school children in poor

nutritional condition and aged three to six years were given a daily supplement of 65 mg. of calcium (as lactate) for four or five months, they gained more rapidly in weight and height than did children not receiving this supplement. Aykroyd and Krishnan (1939) found that when a group of 46 school-children very poorly nourished and six to twelve years of age were given a daily supplement of 130 mg. of calcium (as lactate) for eleven weeks, they also made significant gains over the controls in weight and height.

This stimulating effect, however, was not observed in a similar study carried out in South Africa. Malan and Ockerse (1941) used 92 European school-children, of ages from six to fourteen years; to their everyday diet, which contained about 400 mg. of calcium and 800 mg. of phosphorus, they added a daily supplement containing 500 mg. of calcium and 500 mg. of phosphorus. The experiment continued for three years, although the supplements were given only during school terms, which amounted to about 265 days each year. A control group, numbering 85, received no supplement. No significant differences in weight or height were observed between the two groups.

Further evidence bearing on this issue is also found in South Africa. Dietary surveys have pointed to a wide incidence of malnutrition among the European young, and have drawn attention in particular to the low intake of calcium. In one extensive study on the nutritional condition of European school-children (Union of South Africa Public Health Department 1939) it was revealed that 25% consumed no milk in their diet, and 35% consumed it only occasionally. The cereal content of the diet is often very high, and the amount of phytic acid ingested, especially in the rural areas, where whole-grain bread is often favoured, must be appreciable. Such a diet might be expected to restrict growth. Nevertheless, investigation has shown that the height and weight of the boys for all ages between six and fifteen years are superior to those of English, Canadian, and American boys of the same age; and, with minor limitations, this also applies to the girls (Cluver et al. 1946). The average height of the Bantu is certainly less than that of European South Africans. Nevertheless, poor-white children often consume a diet which resembles that commonly eaten by the rural Bantu (Carnegie Commission 1932), a diet which is high in phytic acid and low in calcium; yet Fox (1934) noted the sitting height of Transvaal poor-white children to be equal to, and in some cases superior to, that of American children of the same age-group *selected* for their good or excellent nutritional status.

Evidently, in the presence of plentiful sunlight, a diet low in calcium, even when accompanied by a high intake of phytic acid, need not prevent excellent growth in

European children. The extent to which height may be restricted specifically by a low intake of calcium, in countries where less favourable conditions of radiation prevail, has not been established.

In conclusion, it cannot be emphasised too strongly that, though it is apparent that good growth and freedom from rickets may prevail on diets which contain little calcium, this must not be interpreted as suggesting that low intakes of this element are considered to be satisfactory, or that higher intakes would be without nutritional advantage.

SUMMARY

Cereals and certain cereal products contain a substance, recently identified as phytic acid, which, under certain conditions, is anticalcifying to dogs. It has been widely accepted that this acid is also anticalcifying to man, the belief being that in the intestinal tract this acid, under certain conditions, precipitates calcium, and, by reducing the amount available for absorption, restricts growth and even causes rickets.

Experimental evidence suggests that, though phytic acid has an immediate disturbing effect on the retention of calcium, the disturbance is not permanent. Considerable caution is required in the interpretation of the experimental evidence in terms of practical nutrition.

When rickets was very common, able clinicians did not distinguish between the rachitogenic effects of oatmeal rich in phytic acid and of white bread free from phytic acid. This fact militates against the critical importance assigned to phytic acid in the ætiology of human rickets.

In Scotland, when the traditional diet contained a large amount of phytic acid and probably little calcium and vitamin D, it has not been established that rickets was widespread.

In tropical and semitropical countries, where advantage is taken of the abundance of vitamin D to be derived from radiation, a high intake of phytic acid, even in the presence of a low intake of calcium, seems to present no problem in so far as rickets is concerned.

In Eire a war-time rise in the incidence of rickets took place at about the same time as the staple bread was changed from white to whole grain, involving a considerable increase in the intake of phytic acid. It is clear, however, that the incrimination of phytic acid is far from conclusive.

Where there is plenty of sunlight, a diet low in calcium, even when accompanied by a high intake of phytic acid, need not prevent excellent growth in European children.

Since cereals and their products are of such profound importance in human nutrition, it seems reasonable to insist that any nutritional stigma attached to their

consumption should be based on conclusive evidence. From the evidence discussed here it appears that the importance of phytic acid as an anticalcifying factor in human nutrition has not been established.

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Letter to the Editor

Growth Rate in Relation to Calcium Losses Through Sweat

Dear Sir:

Experimental studies have indicated that under conditions of high temperature calcium losses through sweating may reach several hundred milligrams *per diem*.[1,2] The F.A.O.-W.H.O. Expert Committee on Calcium Requirements,[3] while recognizing the existence of this avenue of loss, considered the present evidence inadequate to warrant definite recommendations for the relevant populations. Consolazio and his associates,[2] however, considered the information available sufficiently convincing to recommend increased allowances for those who dwell in areas where the climate is hot, especially when they are accustomed to hard physical work. Specifically, these investigators point to the lower rate of growth in indigenous populations in the tropics and semi-tropics and suggest that the inferiority stems, at least in part, from the habitually high losses of calcium sustained during sweating.[2]

Assuming that the level of calcium intake is critical for growth, then to demonstrate the need for an increased requirement, evidence must be forthcoming that those who live in areas where the climate is hot grow slower than those who live in cooler regions, other factors of course being equal, such as ethnic group, diet and prevalence of infections. Therefore, we studied the growth rate and other parameters in South African Bantu school children living in districts which differ markedly in temperature. In trying to obtain strictly comparable groups, numerous difficulties were encountered. Since the ultimate height at maturity differs among ethnic groups,[4] examinations must necessarily be confined to subjects in the same group. Although the selection of appropriate hot and cooler regions, differing in annual mean maximum temperature from 10 to 12°F., presented little difficulty, dietary differences (the consumption of vegetables and fruit being somewhat higher in the warmer regions) and parasitological differences presented some problems. For example, in some *highveld* regions, helminths are virtually absent; but in the *lowveld* regions, although ascaris may not be common, hookworm and two types of bilharzia (Schistosoma haematobium and mansoni) must be reckoned with.[5] In addition regional tribal practices cannot be ignored.[6] Thus, we found that in many areas girls weighed much more than boys of the same age; in some schools, the mean difference at fifteen years of age is as much as 15 pounds. We could not find an explanation for this.

In a number of regions our studies have been confined to groups of children with a similar status in respect to protein (using the urinary total nitrogen : urea nitrogen ratio as an index), and to calcium (using the urinary calcium : creatinine ratio as an index). In the schools we investigated, calcium intake was estimated to be almost invariably less than 450 mg. *per diem*. Differences in intake in different regions were found to be variable but slight.

After repeated attempts we have been forced to recognize the fact that it is almost

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out of the question to secure fully comparable groups which differ *only* in environmental temperatures. Nevertheless, although we have not yet found a solution to this problem, we would like to describe our present progress and to discuss the implications raised. The best results have been obtained from studies on 850 Zulu children in three schools located in a hot region (2,500 feet above sea level) adjacent to, and south west of, the Kruger National Park; and 900 Zulu children from three *highveld* schools (about 7,000 feet above sea level) in the region of Belfast, Eastern Transvaal. In these contrasting regions, average mid-day temperatures over a three month period (summer-autumn) were 84°F. and 60°F., respectively. We did not find the expected differences in the mean values for height and weight of the groups studied. Boys and girls, fifteen years of age, who lived in the hot region had an average height of 63.24 inches and average weight of 111 pounds; those who lived in the cooler regions had an average height of 61.75 inches and an average weight of 108 pounds.

We tried another approach to the problem by studying 700 school children (Zulus) in one of the hottest parts of the Republic, namely, Komatipoort, in the Crocodile River Valley, Eastern Transvaal. Mean mid-day temperature for the same three month period was 88°F. Both types of bilharzia are present in over half the children, and hookworm is present in about 10 per cent. Yet these children were found to be as tall and as heavy as the average Zulu school children (800 examined) in one of the Bantu townships near Johannesburg (6,000 feet above sea level, cool winters, warm summers) where the average mid-day temperature for the period cited was 74°F. These observations do *not* imply that there is no handicap attached to parasitism, but simply that good growth *can* prevail under adverse environmental circumstances. Boys and girls at fifteen years of age averaged 63.50 and 61.50 inches in height, and 109 and 107 pounds in weight, respectively, in Komatipoort, and 63.75 and 61.125 inches in height, and 101 and 104 pounds in weight, respectively, in Johannesburg.

Finally, we would like to mention another type of investigation which was undertaken a few years ago in two groups of Bantu children living in the hot regions of the south central Kalahari Desert, Bechuanaland. One group of 100 boys (twelve to fifteen years of age) studied was habituated to drinking brakish well water which supplied approximately 300 mg. calcium *per diem;* the other group of children, of equal number and age, drank from wells of soft water, which supplied roughly about 50 mg. of calcium daily. Nutritional conditions in both areas were similar. No differences were found in the mean height and weight of the children studied in the two regions. Boys at fifteen years of age averaged 60.25 and 60.5 inches in height and 98 and 99.5 pounds in weight, respectively.

We wish to reiterate that these studies are not final, since more diligent search (as the opportunity offers) may reveal more suitable groups of school-children for comparative investigation. Nevertheless, since the results obtained in respect to differences in growth rate are negative, extreme caution should be used in extrapolating the results of short-term experimental studies from one population group to another. Recommendations for changes in nutrient intake, based on the results of experimental studies, which conflict with, or which have not yet received unequivocal support from field observations, should not be made without a careful reappraisal of the interpretations and applications of the former studies. Until there is appropriate evidence, such recommendations, made primarily as a precautionary measure, are unwarranted. It is a simple matter for affluent nations to recommend the addition of this or that nutrient to staple diets to offset the noxious effect of suspected deficiencies. However, when huge, underprivileged populations are concerned, nutritional supplementation or enrichment must be viewed in the light of what expenditure is likely to produce the most beneficial results.[7] Understandably, the provision of adequate calories and protein foods must be

[7] WALKER, A. R. P. Problems in nutritional supplementation and enrichment. *Am. J. Clin. Nutrition*, 12: 157, 1963.

accorded priority long before the addition of calcium can be considered, especially in view of the paucity of knowledge on its requirements and deficiency stigmata.[3]

Furthermore, when considering recommendations for an increased calcium intake, many other aspects of the problem must be considered: (1) Optimum rates of growth have not yet been defined; certainly they are not maximum rates. Experimental studies in animals have demonstrated that a slower rate of growth is not essentially prejudicial and may, indeed, be beneficial. Admittedly, when compared with local white children, all Bantu children studied are shorter in height and lighter in weight; but, in the absence of overt deficiency disease, whether or not their enjoyment of good health is adversely affected on this account is debatable. (2) In an underprivileged population, children of the more prosperous moiety grow faster than those in the poorer section.[8] It is not known, however, to what extent ultimate height at maturity is correspondingly affected. That an ethnic factor operates in this respect is not doubted, for example, in the United States, an early study indicated that Scots are taller than Italians;[9] surely this does not essentially imply undernourishment in the latter group during growth. (3) Diets low in calcium are usually low in other nutrients as well; to suggest or imply that calcium deficiency is chiefly responsible for retarded growth is not justified.[4] (4) It is conceivable that a habitual accentuated loss of calcium from sweating may be met simply by increased absorption or reduced excretion, in which case daily retention may be affected little.

Weight, height and other measurements have been made on fairly comparable groups of Bantu children accustomed to different environmental temperatures. No significant differences were found in the two groups. Search has not yet afforded wholly comparable groups suitable for study; however, the observations made thus far do not indicate that the higher calcium losses through sweating in hot regions compared with the losses in cooler regions necessitate an increased intake of the element.

ALEXANDER R. P. WALKER, PH.D.
and B. D. RICHARDSON
Human Biochemistry Research Unit
South African Institute for Medical Research
Johannesburg, South Africa

[8] KAHN, E. and FREEDMAN, M. L. The physical development of a privileged group of African children. *South African M. J.*, 33: 934, 1959.

[9] PATON, D. N. and FINDLEY, L. Poverty, Nutrition and Growth. Special Report Series No. 101. London, 1926. Medical Research Council.

The journal including this letter has just been received. The photostat has therefore been pasted over the stencilled Ms.

GROWTH IN HOT AND COOLER CLIMATES IN RELATION TO LOSS OF CALCIUM BY SWEATING.

Experimental[1,2] studies have indicated that under high temperature conditions, losses of calcium through sweating may reach several hundred milligrams per diem. The F.A.O. - W.H.O. Expert Committee on Calcium Requirements,[3] while recognizing the existence of this avenue of loss, considered that present evidence was inadequate to warrant the making of definite recommendations for populations among whom excessive losses are likely to occur. Consolazio and associate workers,[2] however, consider that available information is sufficiently convincing to recommend increased allowances for dwellers in hot climates, especially for those accustomed to hard physical work. Specifically, these workers point to the lower rate of growth in indigenous populations in the tropics and semi-tropics and suggest that the inferiority stems, at least in part, from habitually high losses of calcium sustained during sweating.[2]

To demonstrate an increased calcium requirement, evidence must be forthcoming that children in hotter climates grow slower than those in cooler regions, other factors of course being equal, such as ethnic group, diet, prevalence of infections, etc. In an attempt to throw light on the practical aspects of the problem, we have studied growth rate and other parameters in South African Bantu school children dwelling in districts differing markedly in temperature. In trying to obtain strictly comparable groups, as might be expected, numerous difficulties have been encountered. Since ultimate height at maturity differs in ethnic groups,[4] obviously, examinations must be confined to subjects in the same group. The selection of appropriate hot and cooler regions, differing in annual mean maximum temperature by, say, 10 - 12°F., has presented little difficulty. But,

unfortunately, there are dietary differences in the two types of region, the main difference being a slightly greater consumption of vegetables and fruit in warmer parts. Parasitological differences too are present. In many highveld regions, helminths are virtually absent; but in the lowveld, although ascaris may remain uncommon, there is hookworm, also two types of bilharzia (S. haematobium and mansoni) to take into reckoning.[5] Regarding bacteriological infections, serial studies on stools have revealed the commoness of salmonella and shigella;[6] however, such appear to be present not only in rural, but also in peri-urban and urban areas.[7] Regional tribal practices, of course, cannot be ignored.[8] In many parts we have found that girls weigh much more than boys of the same age; in some schools, at 15 years the mean difference may be as much as 15 lb.; the explanation is not known.

Studies in a number of regions have been confined to groups of children having similar status in respect of protein, using urinary total nitrogen/urea nitrogen ratio as an index, and of calcium, using calcium/creatinine ratio in the urine as an index. In the schools investigated, calcium intake was estimated to be almost invariably less than 450 mg. per diem. The amount of the element contributed by the drinking water was estimated to be roughly 30 mg. per diem. The differences in these two respects in different regions were found to be variable though slight. After repeated attempts we have been forced to recognize that to secure fully comparable groups differing only in environmental temperature is almost out of the question. Nevertheless, until we are able to advance further in our endeavours we would like to relate progress made thus far, and discuss the implications raised. The best comparisons have concerned studies at three schools including 800 Zulu children, in a hot region (2,500 ft. above sea level)

adjacent to, and south west of, the Kruger National Park; and three highveld schools (about 7,000 ft. above sea level), including 900 Zulu children in the region of Belfast, Eastern Transvaal. Average mid-day temperatures over a three month summer-autumn period were 84°F and 69°F. We found, however, no significant difference in mean values for height and weight of the Bantu children studied.

In another type of approach to the problem, we studied 700 school children (Zulus) in one of the hottest parts of the Republic, namely, Komatipoort, in the Crocodile River Valley. Mean mid-day temperature for the above mentioned period was 88°F. Both types of bilharzia are present in over half of the children, and hookworm in about 10%. Salmonella and shigella are as common as in other regions studied. Yet children were found to be as tall and as heavy as average Zulu school children (800 studied) in one of the Johannesburg Bantu townships (6,500 ft. above sea level, cool winters, warm summers), where average mid-day temperature for the period cited was 74°F. These observations certainly do not imply that there is no handicap attached to parasitism, but simply that good growth can prevail under adverse environmental circumstances. In other comparisons Bantu children have greater height and weight in urban than in rural areas.

Finally, we would like to mention another type of investigation, undertaken a few years ago, which concerned Bantu children living in hot regions in south central Kalahari Desert, Bechuanaland. One group of 100 children (12 - 14 years) studied was habituated to very brakish well water supplying approximately 300 mg. calcium per diem; the other group, of equal number and age, drank from wells of soft water, ingesting roughly about 50 mg. of the element daily. Nutritional conditions in both areas were

closely similar. There were, however, no differences in the mean height and weight of the children studied.

We wish to emphasize that the studies undertaken and described are not final, since more diligent search, as opportunity offers, may reveal school-child groups more suitable for comparative study. Novertheless, since negative results have been obtained up to the present in respect of growth rate differences, such surely call in question the wisdom of extrapolating the results of short-term experimental studies from one population group to another habituated in measure to these conditions. When recommendations for changes in nutrient intake, arising from experimental or laboratory studies, be made which either are in conflict with or which do not yet derive unequivocal support from field observations, the interpretations and applications of the former studies should be carefully reappraised. Until appropriate evidence from field studies is forthcoming which demands unequivocally an increased intake of calcium, it would seem unwarranted to make such recommendations primarily for insurance purposes. It is of little moment for affluent nations to recommend the addition of this or that nutrient to staple diets to offset the noxious effect of suspected deficiencies. But when huge underprivileged populations are concerned, nutritional supplementation or enrichment has to be considered in light of what expenditure is likely to produce most beneficial results.[9] Understandably, provision of adequate calories and protein foods must be accorded priority long before the addition of calcium be considered, especially in view of the paucity of knowledge on the requirement and deficiency stigmata of this element.[3]

In Britain during the war years, beliefs on the ill-effects of phytic acid on calcium absorption led to the nation-wide addition of a calcium salt to the staple bread meal.[10] Yet

no unequivocal evidence was, or has yet been, adduced that populations accustomed to a low calcium intake and a high phytic acid intake suffer specifically from calcium deficiency.[11] Recently, it has been put forward that the somewhat lower serum calcium levels which are found in populations accustomed to a low calcium intake imply sub-optimal health and performance, and indicate the need for an increased intake of the element.[12] Yet the implication was not defined, nor was a speculation hazarded on the benefits to health likely to accrue from an increased intake of the element. The recommendation for increased calcium intake to offset loss of the element by sweating in hot climates is a further example of recommending an increased intake of a nutrient to meet and overcome an as yet undemonstrated nutritional need.

When considering the recommendations for an increased calcium intake, it is considered that insufficient attention has been paid to other aspects of the problem which also enjoin caution:- (1) Optimum rates of growth have not yet been defined; certainly they are not maximum rates. Experimental studies on animals have demonstrated that a slower rate of growth is not essentially prejudicial, and may indeed be beneficial. Admittedly, compared with local White children, all Bantu children studied were shorter and lighter; but whether, in the absence of overt deficiency disease, their enjoyment of good health is specifically stigmatised on this account, is debatable. (2) In an underprivileged population, children of the more prosperous moiety grow faster than those in the poorer section.[13] It is not known, however, whether ultimate height at maturity is correspondingly affected. That there is an ethnic factor operating in this respect is undoubted; for example, in the United States, an early observation indicated that Scandinavians are taller than Italians;[14] surely this does not essentially

imply under-nourishment in the latter during growth. (3) Diets low in calcium usually are low in other nutrients; to suggest or imply that calcium deficiency is chiefly responsible for a slower rate of growth is unjustified.[4] (4) It cannot be ruled out that an accentuated loss of calcium from sweating is met simply by increased absorption, or reduced excretion, and that the daily retentions of the element needed for growth are little affected.

S U M M A R Y .

Weight, height, and other measurements have been made on somewhat comparable groups of Bantu children habituated to different environmental temperatures. No significant differences in the data on the two groups were found. Search has not yet revealed wholly comparable groups for study; however, the results obtained thus far do not support the view that higher losses of calcium caused by greater sweating in hotter regions necessitate an increased intake of the element.

ALEXANDER R.P. WALKER. Ph.D.

B.D. RICHARDSON.

SOUTH AFRICAN INSTITUTE FOR MEDICAL RESEARCH,

JOHANNESBURG, SOUTH AFRICA.

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NOTES

Letters to the Editor

Sir:

In a special article (*Nutrition Reviews* **15**, *257* (*1957*)) D. M. Hegsted indicated the need for a re-examination of the situation concerning the present high recommended intakes of calcium. Supporting his view (*Ibid.* **16**, *31* (*1958*)), I questioned the wisdom of recommending luxus intakes of the element in the absence of specific deficiency stigmata.

In a recent study on pathological grading and chemical composition of aorta from Bantu and white subjects, we drew attention to the far higher concentration of calcium in white compared with Bantu aorta from middle age onwards, and even in aorta of equal pathological grading (M. Anderson *et al.*, *A. M. A. Arch. Path.* **68**, *380* (*1959*)). In a paper just published, A. E. Hirst Jr., *et al.* (*Arch. Path.* **69**, *578* (*1960*)) also have noted the far greater incidence and severity of calcification lesions in aorta from Los Angeles whites compared to Indians in South India. Both the latter population and the South African Bantu have low calcium intakes, lesser severity of aortic and coronary lesions, and a much lower mortality from coronary heart disease.

The precise bearing of arterial calcification on mortality from coronary heart disease is not known. But if, to ward off death from this cause, a reduction in the amount of fat consumed is recommended, would it not be logical also to recommend a modicum of reduction in the present high calcium intakes ingested by more privileged populations?

ALEXANDER R. P. WALKER
South African Institute for Medical Research
Johannesburg, South Africa

Dear Sir:

The review of the effect of antioxidant on vitamin E deficiency in chicks (*Nutrition Reviews* **17**, *340* (*1959*)) prompts the following comments which may be useful, since much of our work was not submitted to journals normally read by many investigators in animal nutrition.

In all species tested to date (man: *Am. J. Clin. Nutrition* **4**, *408* (*1956*); **8**, *451* (*1960*); *A. M. A. Arch. Neurol.* **1**, *312* (*1959*); the chick: *Proc. Soc. Exp. Biol. Med.* **102**, *575* (*1959*); *A. M. A. Arch Gen Psychiat.* **1**, *420* (*1959*); the rat: *J. Nutrition* **72**, *Nov. issue* (*1960*)), the level of alpha-tocopherol required to inhibit reactions attributable to vitamin E deficiency were functions of the amounts of peroxidizable compounds present in the diet or in the tissues. For example, little if any added tocopherol is required when only small amounts of polyunsaturated fatty acids are present, but the requirement for tocopherol increases markedly as the level of linoleic acid in the diet is increased.

Accordingly, one should never interpret an experiment on tocopherol need without evaluating how much total polyunsaturated fatty acid is in the diet. It should be emphasized that even lard, which normally contains about 10 per cent linoleic acid (and much more if the pig was fed unsaturated fats), can provide as much linoleic acid at a 20 per cent level in the diet as corn oil at a 4 per cent level. Both of these levels of fat are sufficient to produce encephalomalacia in most chicks deprived of tocopherol since they provide more than 2 per cent linoleic acid in the diet.

The fatty acid profile of all of the tissue lipoproteins and phospholipids tested today are influenced by the levels of various fatty acids in the lipids consumed, either from the diet or as a result of previous ingestion. The effect of diet on tissue lipid composition, which hog raisers have con-

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Does a LOW *Intake of* CALCIUM *Retard* GROWTH *or Conduce to* STUNTEDNESS?

By A. R. P. WALKER, M.SC., PH.D.*

IT IS ALMOST universally accepted that the level of calcium intake of the young influences their rate of attainment of height. According to Sherman,[1] steady growth in children requires a high intake of the element. Concerning low intakes, Venar and Todd[2] and, more recently, Stearns,[3] maintain that there is ample evidence that deficient intake or utilisation of calcium and other mineral salts result in slowing down growth and lengthening of growing period. Several authorities, moreover, go further and take the view that a low intake of calcium conduces to stuntedness.[4-10] In tropical and semitropical countries, low calcium intakes are usual, and the calcium-phosphorus ratio occasionally is as wide as 1:10. The retarding effect on growth would therefore be expected to be well marked, and in this connection, McCance and Widdowson[11] have referred to the smallness of the children from such parts, linking up this characteristic with the prevailing "sub-optimum level of calcium nutrition." Despite the general acceptance of this particular role of calcium, and the assurance with which the belief is often stated, no one appears to have investigated its validity.

Growth, of course, requires other dietary components in addition to calcium. Furthermore, growth is influenced certainly by hereditary, and possibly other factors.[12] Hence, where retardation is demonstrable, it could be due, not only to a low intake of calcium, but to the operation of other single or multiple dietary or non-dietary factors. Ideally, to supply an unequivocal answer to this question of the role of calcium intake in growth, it would be necessary to have a single homogenous population among whom comparable age groups differed only by one factor, i.e., level of calcium intake. The more two groups differ from this situation, due to the presence of other variables, the greater will be the uncertainty of the validity of the conclusions drawn. Needless to say, this ideal state is never observed, for neither homogenous population groups nor diets of widely varying calcium content though otherwise nutritionally adequate are encountered in practical human nutrition. At the outset, therefore, it will be apparent that it is highly improbable that a clear answer can be given as to whether level of calcium intake is or is not of critical importance in the attainment of height.

It is now proposed to illustrate and amplify the difficulties described by referring firstly, to the height of children of the same age; next,

From the Human Biochemistry Unit, South African Institute for Medical Research, Johannesburg, and South African Council for Scientific and Industrial Research.

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* Head of Human Biochemistry Unit, of the South African Institute for Medical Research, Johannesburg, and the South African Council for Scientific and Industrial Research.

to height of adults at maturity; and lastly, to studies bearing on the use of calcium supplements under controlled conditions.

The Height of Children of the Same Age

Several authorities in different parts of the world, for example, Orr[13] in Great Britain, Nicholls and Nimalasuriya[14] in Ceylon, and le Riche[15] in South Africa, have shown that children from poor families are less tall than children of the same age from better class homes. Differences in the diet consumed, especially in regard to calcium intake, are usually considered to bear chief responsibility.[3,7,16,17] However, as far as one is aware, no critical evidence has yet been adduced to show that the low calcium intake of the less tall sections is *specifically* implicated in retarding growth.

There is no dispute that Western children are taller than indigenous children of the same age groups dwelling in tropical and semitropical regions. This general observation has been made by Stearns,[3] and considerable supporting evidence is available, for example, the recent investigation of MacKay and Martin[18] on a tribe of Kenya Bantu. Yet the phenomenon is not invariably observed, for in the study of Welbourn,[19] it was reported that the mean height of the Kampala Africans examined at 8 years was greater than that of local European children of the same age group and, incidentally, coming from very good homes. It must be appreciated that the value of any relevant information on non-White groups is limited because (1) their ages are known with far less certainty than is the case with Western children; (2) little knowledge is available on their periods of growth spurts, whether they coincide or not with those of Western children; and (3) it is not known whether the increases in height of children of all classes which have occurred in Europe, North America, India, and Japan have yet affected the African races.[20] But quite apart from these uncertainties, there appears to be no evidence that the low calcium intake of the child populations of tropical and semitropical countries is specifically involved in retarding their rate of attainment of height.

Height at Maturity

When one considers final height, the uncertainties referred to fall away. Orr[21] has pointed out the strong body of opinion which considers that adult height is not correlated with nutrition, and that stature and configuration of body are inherited and cannot, to any significant extent, be affected by diet. Temporary retardations may occur as in wartime or in famine, but the growth urge is believed to be so strong that the ultimate predestined stature is attained on any ordinary diet. There is much evidence that with growing children, temporary dietary restrictions do, in fact, become nullified in time after resumption of the previous habitual diet. This was observed, for example, with the German children of World War I,[22] also with the French children in the last war.[23] On the other hand, the observations of Shapiro[24] on the physical characteristics of Japanese immigrants and their offspring in Hawaii are pertinent; he found an average difference of 4.1 and 1.7 cm. in the height of adult males and females, respectively, in favour of Hawaiian born, which showed that heredity is not the only factor determining stature at maturity. The different observations cited merely underline the complexity of the subject by indicating the almost insuperable difficulties inherent in efforts to assess the relative importance of the individual influencing factors.

Nevertheless, it would seem reasonable to suggest that if the level of calcium intake is a *critical factor* in the attainment of height, then low consumers of the element should be invariably stunted. But what is understood by being stunted? By how many inches must a population group be shorter than a better fed Western population group before the former may be labeled as stunted? McLester and Darby[25] have defined *leanness* as a condition of the body in which weight is 15 per cent or more below normal. Were the same proportion valid for height, then taking 6 ft. as an arbitrary height, a person would have to be less than 5 ft. 1 in. before being described as undersized or stunted. Using this reckoning, only certain groups of pygmies could be put into

TABLE I

The Height of Population Groups at Maturity

Observer	Population group	No. examined	Height
Turner[26] (1910)	South African Bantu		
	East Coast Bantu	1337	66.5 in.
	Transvaal Basuto	521	66.0 in.
	Cape Province Bantu	680	66.25 in.
Walker[27] (1954)	East Coast Bantu	1100	66.35 in.
	Transvaal Basuto	650	66.25 in.
	Cape Province Bantu	720	66.1 in.
Carlson[28]	United States Army recruits	800,000	67.5 in.
Clements and Pickett[29]	Scotsmen, National Service recruits	1303	66.82 in.

the latter category. As far as I am aware, no precise figure has yet been advanced to define stuntedness. However, to illustrate that low calcium consumers are certainly not all stunted at maturity, Table I has been compiled, in which data on three South African groups are given, also two Western groups.

The South African Bantu groups were composed of mine-labourers who were measured at the Witwatersrand Native Labour Association Headquarters in Johannesburg, the clearing centre through which pass over a quarter of a million workers annually. The groups were selective only in so far as there is no compulsion to work on the Mines. But the tribal social status of the individual is so enhanced, and, moreover, the remuneration accruing is so apt a way of saving money to buy cattle for the acquiring of wives (the *lobolo* system), that only serious disability prevents volunteering for service. The differences between the two sets of Bantu data are not significant; furthermore, the latter data[27] refer only to *new* adult recruits, thereby obviating the effects of the excellent diet provided by the Mines. The data on the American and British adult males refer to unselected subjects.

The mean heights of the South African Bantu males from the regions mentioned in all cases are less (roughly 1 and 2 per cent respectively) than the mean values given for the two groups of White subjects. But the inferiority is surely insufficient to label the former people as stunted, despite habituation to a low calcium diet, i.e., 200–450 mg. *per diem*.[30–35] While it is probable that the more plenteous sunlight enjoyed by dwellers in tropical and semitropical countries compensates in part for their low intake of calcium, the fact remains that the latter handicap apparently has not markedly prejudiced the height of the adult Bantu groups cited.

There is, however, one Bantu group whose intake of calcium is relatively high. In Nyasaland, Barker[36,37] reported that potashes (plant ashes) are included in the customary diet almost every other day. The ashes of similar plants found in the Union contain approximately 2–5 per cent of calcium.[38] According to Barker (*loc cit*), an adult may ingest an average of 2 oz. ashes *per diem*, this amount contributing a supplement of over a gram of inorganic calcium. While it would be imprudent to lay stress on the accuracy of these figures, there is no doubt that the Nyasaland Bantu with his supplement of calcium salts ingests a larger amount of the element compared with the South African Bantu, many regional groups of whom do not use potashes. At the Witwatersrand Native Labour Association Headquarters, previously referred to, the height of 480 consecutive Nyasaland adult male new recruits was found to average 65.7 in., a figure slightly less (though not significantly so) than the data for the Bantu groups given in Table I. The important point would seem to be that the probably large difference in the calcium intake of these Bantu populations has not promoted a marked difference in height at maturity.

The Effect of Calcium Supplements on Height Increments

In seeking more information concerning the question at issue, a further avenue of approach is to examine evidence bearing on the use of calcium supplements under controlled conditions. The following investigations are thus of interest: the first, on African boys, and the second, on Indian children.

In Kenya, at Kabete Reformatory, Orr and Gilks[39] investigated the effect of various dietary supplements on the growth of African

boys, of ages 10–17 years, engaged on farm work. Each of the four groups of 40 boys received one of the following diets. (1) The basal diet was composed of maize, beans, potatoes, ghee, and salt; it provided 3270 calories, 112 Gm. protein, and *560 mg. calcium* per diem. (2) The second group received the basal diet plus $^3/_4$ lb. maize, providing in all, about *620 mg. calcium.* (3) The third group consumed the basal diet plus $^1/_4$ lb. maize, which included 2 Gm. bone flour—providing in all about *980 mg. calcium.* (4) The fourth group received the basal diet plus 1 pint skimmed milk—providing in all about *1250 mg. calcium.* The experiment lasted for six months, although the measurements, etc., were continued for a further six months. The results obtained were as follows:

TABLE II

The Effect of Various Food Supplements on Height Increments

Diet	Supplement period. Average increase in height after 6 months	No supplement period. Average increase in height after 6 months
(1) Basal diet (560 mg. calcium)	0.71 in.	0.66 in.
(2) Basal diet plus maize (620 mg. calcium)	0.97 in.	0.79 in.
(3) Basal diet plus maize and bone flour (980 mg. calcium)	0.94 in.	0.76 in.
(4) Basal diet plus skim milk (1250 mg. calcium)	0.99 in.	0.76 in.

The calcium present in the bone flour is known to be available for absorption and metabolism.[40] If the height of the boys was being specifically retarded by lack of calcium, the height increments in groups (3) and (4) would be expected to be greater than in group (2). This was not the case. Within its experimental limitations, the investigation does not indicate that the low calcium intake in group (2), which amounted to about half the recommended allowance, was prejudicial to the rate of growth of the boys. Orr and Gilks[39] suggested that the additional increments in height in the supplemented groups were probably due to the extra calories supplied.

In an investigation carried out in India, Aykroyd and Krishnan[41] gave 36 children, of ages 3 to 6 years, a daily supplement of 65 mg. calcium (as lactate) for a period of 4 to 5 months. The children, in poor nutritional condition, and habituated to an unspecified but presumably small amount of calcium, gained more rapidly in weight and height than did 40 similar subjects not receiving the supplement. Later,[42] in 1939, these workers reported that when a group of 46 poorly nourished Indian children, of ages 6 to 12 years, were given a daily supplement of 130 mg. calcium (as lactate) for 11 weeks, they also made significant gains over 44 controls in both weight and height. The results of the two investigations are summarised in Table III.

TABLE III

Increases in Height of Indian Children with and without Calcium Lactate Supplements

Age	Period	Average increases in height	
		Calcium lactate group	Control group
3–6 years	4–5 months	0.63 in.	0.42 in.
6–12 years	11 weeks	0.86 in.	0.72 in.

The conclusion that the increased height increment was due *specifically* to a previous deficiency of calcium seems self-evident. Nevertheless, there are two points which argue against its ready acceptance. Firstly, the calcium lactate groups gained weight more rapidly than did the control groups, indicating that the supplemented groups consumed more food. The responsibility for the additional increase in height may thus have been shared between the calcium lactate supplement and the additional food eaten; to ascribe it wholly to the former is unwarranted. Secondly, it is well known that many compounds stimulate the appetite, directly or indirectly, but such an effect surely need not arise from their previous deficiency. Thus, the spectacular acceleration in growth produced in various animals by antibiotics (recently reviewed by Braude *et al*).,[43] cannot be attributed to a previous dietary deficiency of these substances.

From the experiments described, therefore, it cannot be assumed with certainty (1) that the acceleration of growth arose from calcium supplementation *per se:* (2) that a previous deficiency of calcium prevailed; and (3) that calcium was the only key which fitted the metabolic lock and released or promoted the additional increases in heights.

Discussion

It must be reiterated that the sole point at issue in this paper is whether population groups or races ingesting an amount of calcium *per diem* considerably less than the recommended allowance, are specifically stigmatised by retarded attainment of height, and by stuntedness at maturity. From what has been discussed, and as far as one can tell from the large volume of other relevant information, there appears to be no evidence that differences in the height of children or of adults are influenced by differences in calcium intake. It is, of course, well known that restriction of calcium intake in an otherwise adequate diet when fed to growing rats, *does* cause retardation of skeletal development.[44] There is little information available, however, on the low level where such retardation becomes operative in man. Apart from gross undernutrition, as in famine conditions, it is submitted that the critical level lies *below* the wide range of calcium contents of everyday diets consumed in different parts of the world.

Summary

It is widely accepted that in humans a low intake of calcium prejudices the rate of attainment of height and makes for ultimate stuntedness. There are, however, so many factors, dietary and non-dietary, which influence growth, that a precise assessment of the particular role of calcium is well nigh impossible.

Children from poor homes, and probably with a relatively low calcium intake, are certainly inferior in height compared with better class children of the same race and country. In addition, usually, though not invariably, indigenous children from tropical and semitropical countries, habituated to a low intake of calcium, are inferior in height compared with Western children. In neither case, however, is there evidence that differences in calcium intake are specifically implicated.

Where calcium supplements have been fed for short periods to children and youths accustomed to intakes of calcium less than the recommended allowances, there appears to be no critical evidence that these additions have specifically produced increments in height beyond such observed in controls.

The conclusion is reached that it has not been established that calcium intake *per se* is of importance in regulating height. It is suggested that apart from gross undernutrition, the critical intake of calcium below which retardation of growth occurs, lies *below* the wide range of calcium contents of everyday diets consumed in different parts of the world.

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Resumen

¿ Conduce un consumo escaso de calcio a un retraso del desarrollo y crecimiento insuficiente?

Es comunmente aceptado que un consumo escaso de calcio perjudica, en el hombre, a la velocidad del desarrollo de la estatura y conduce finalmente al crecimiento insuficiente. Hay, sin embargo, tantos factores, así dietéticos como no dietéticos, que influyen sobre el crecimiento, que resulta casi imposible determinar con exactitud el papel del calcio.

Los niños de hogares pobres con un consumo probablemente insuficiente de calcio son ciertamente de estatura inferior, en comparación con niños más afortunados de la misma raza y del mismo país. Es, ademas, un hecho común, si no invariable, que los niños indígenos de países tropicales o semitropicales, habituados a un consumo escaso de calcio, sean de estatura inferior, comparados con niños occidentales. En ningún caso, sin embargo, hay evidencia de que diferencias en el consumo de calcio sean específicamente implicados en este retraso del desarrollo.

Ahí donde suplementos de calcio se han suministrado durante cortos períodos a niños y jóvenes acostumbrados a consumir cantidades de calcio menores que las recomendadas, no parece exista evidencia de que estas adiciones, específicamente, hayan producido incrementos de estatura mayores que los observados en sujetos de control.

Se concluye que no queda establecido que el consumo de calcio sea, por sí solo, de importancia en la regulación de la estatura. Se sugiere que, aparte de la hiponutrición manifiesta, el nivel crítico de calcio en la dieta, por debajo de la cual ocurre una retardación del crecimiento, se halla *por debajo* de los límites anchos del contenido de calcio de las dietas ingeridas diariamente en varias regiones del mundo.

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Studies on Human Bone from South African Bantu Subjects

II: Histopathological Changes in the Ribs of South African Bantu Infants

By JOHN HIGGINSON

IT HAS been shown, in Part I of this study, that the chemical composition of ribs from Bantu subjects (excluding rachitic infants) is similar to that of Europeans, although the former race is accustomed to a diet judged to be unsatisfactory by European standards.[1] The results, however, do not imply that the proportion of total bone to body weight is similar for both races, nor that bone growth is normal. As few investigations on bone have correlated chemical and histological findings, the present paper describes our histopathological observations on the ribs of a series of Bantu subjects, including the 44 Bantu infants from the previous study. Since abnormalities due to disease or faulty nutrition are most likely to be apparent in infants showing rapid growth, almost exclusive attention has been devoted to this age group.

MATERIALS AND METHODS

The costochondral junction of the fifth rib was examined in 80 Bantu infants dying in hospital over a two-year period. Subjects were selected in that clinicians tended to request autopsies on children suffering from nutritional syndromes, and the limited facilities available did not permit a necropsy on all infants dying in hospital. Seventy ribs were from subjects under 2 years of age; the remaining 10 were from children between 2 and 4 years, inclusive. The primary causes of death are given in Table 1. In addition, thirteen ribs from European infants, all under 2 years of age, were examined. Ribs from a small number of Bantu adolescents and adults were also sectioned and examined.

The ribs were fixed in 10% formalin and mainly decalcified in sodium citrate-formic acid solution, and embedded in celloidin and paraffin. A few ribs were decalcified in 5% nitric acid. Sections were cut at 6 μ and stained with hematoxylin and eosin.

HISTOPATHOLOGICAL OBSERVATIONS

Infants

On section of the costochondral junction, nonspecific growth depression was the commonest change observed, this being noted in 40 ribs (50%). It was most marked in cases of severe malnutrition (kwashiorkor), the pathology of which has recently been reviewed by Davies.[2] In brief, this disease is believed to be

From the Department of Pathology, Baragwanath Non-European Hospital; and the South African Institute for Medical Research, Johannesburg, South Africa.

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TABLE 1.—*Primary Cause of Death*

	Males	Females	Total
Kwashiorkor	12	8	20
Gastroenteritis	7	11	18
Tuberculosis	2	5	7
Respiratory disease	5	6	11
Miscellaneous	11	13	24
Total	37	43	80

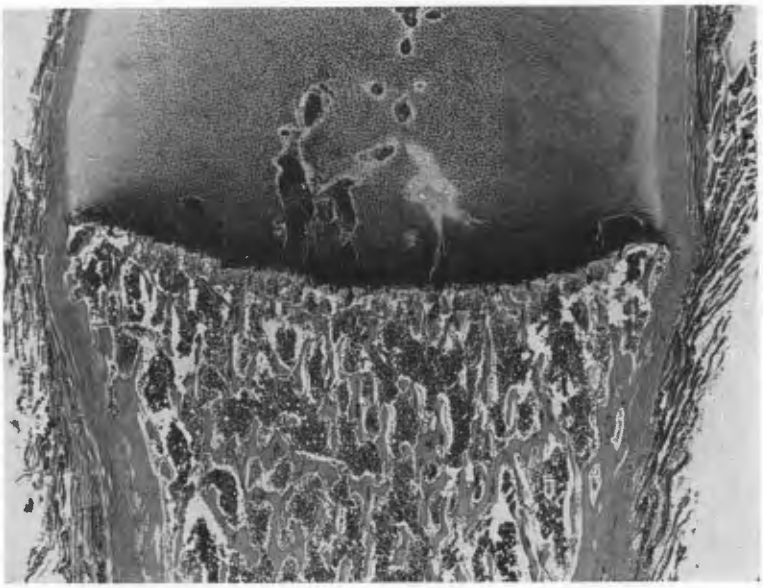

FIG. 1.—Costochondral junction from case of kwashiorkor showing marked growth depression. Note almost complete absence of capillary invasion of the metaphysis. Bantu, female, 8½ months. Ehrlich's hematoxylin and eosin, × 10.

due to malnutrition and is widespread among African children after weaning. It is associated with a fatty liver and general visceral atrophy. However, as little has been published on the bone pathology in this condition, we are presenting our findings in some detail.

Kwashiorkor. In the 20 infants dying from this disease, the ribs usually showed some degree of "beading" on naked eye examination. Several ribs also appeared more malleable and easier to cut than those from comparable European subjects.

Microscopic examination revealed the characteristic picture of growth depression, which was observed to a varying degree in all but two ribs. In cases with the most marked changes, the zone of endochondral ossification was reduced sometimes to less than half the expected width, and the area of calcified cartilage also appeared decreased. The number of both columnar and hypertrophied cartilage cells was diminished, and the cells themselves were flattened and contained pyknotic nuclei. In the subepiphyseal zone, vascular invasion of

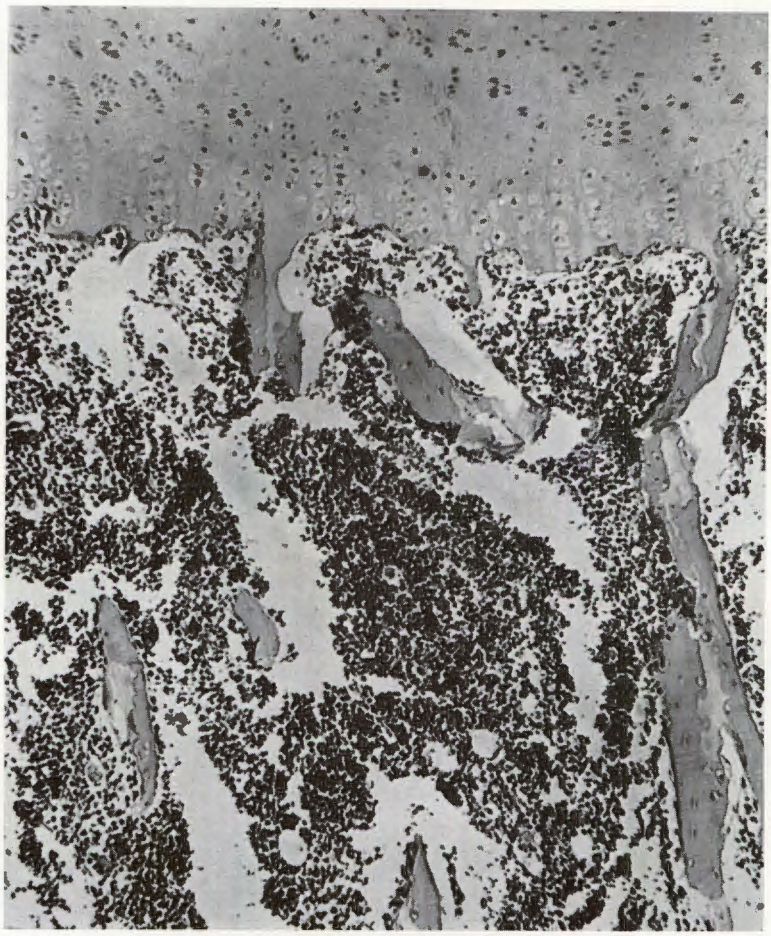

FIG. 2.—High power view of the same rib as above. Mayer's hemalum and eosin, × 95.

the calcified cartilage had ceased and the metaphyseal trabeculae were absent or short and club-like (Figs. 1 and 2). Sometimes, the spaces formed by the degeneration of hypertrophied cells contained a plug of ossified material, and the spaces were separated from each other by a projection of ephiphyseal cartilage covered by a thin layer of bone. In some cases, especially in older infants, this bar of transverse bone formation was sufficiently marked to be called a "line of arrest." Osteoblasts were relatively few and spindle shaped, and osteoclastic activity was slight or absent. In the shaft, the trabeculae appeared attentuated and reduced in number (Fig. 4), being surrounded by scanty osteoblasts. In some cases bone formation appeared almost confined to the cortex (Fig. 4).

In ribs where growth depression was less marked, the changes were confined to irregular capillary invasion of the epiphysis and reduction in the zone of proliferative cartilage cells. In some cases a few of the spaces formed by the degenerated hypertrophic cartilage cells were lined by a very small amount of osteoid. But osteoid formation in the shaft was not obvious. Decrease in the

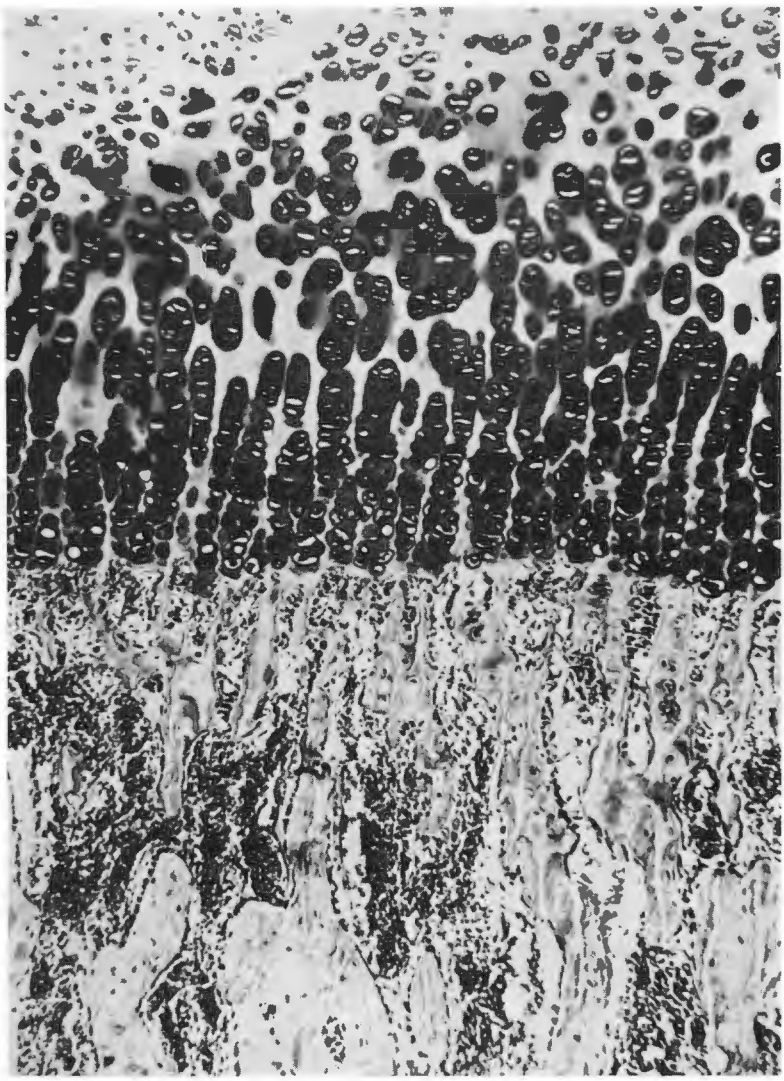

FIG. 3.—Normal costochondral junction from European child of 12 months, dying from gastroenteritis. Ehrlich's hematoxylin and eosin, × 95.

zone of cartilage proliferative cells was still the most obvious lesion in these cases.

In many ribs the bone marrow appeared unaffected and extended to the metaphyseal line, but in a third of these ribs it was slightly edematous. In one case, considerable edema and degeneration of the marrow were observed, similar to the appearances reported in starvation.[3]

In the remaining two ribs from kwashiorkor patients, definite rachitic changes were apparent. In the one case the infant had been in hospital for 45 days. He had improved markedly and was gaining weight on a high protein diet, when death occurred from intercurrent bronchopneumonia. No prophylactic anti-rachitic treatment was given during hospitalization. On admission, an x-ray of

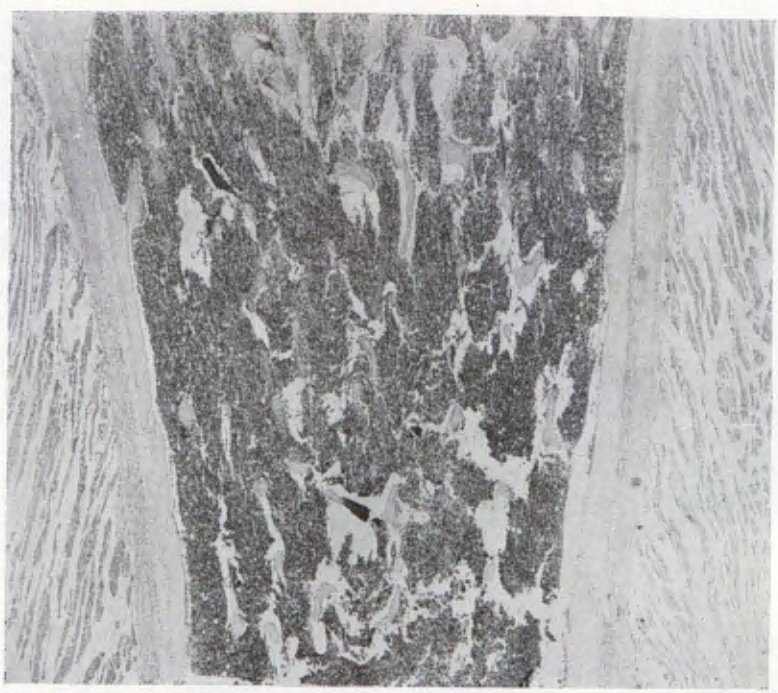

FIG. 4.—Shaft of fifth rib from patient dying from kwashiorkor. A marked diminution in the number of bone trabeculae is observed in comparison with the rib in Figure 5. Bantu, male, 13 months. Mayers hemalum and eosin, × 16.

the ribs showed no radiological evidence of rickets, but at autopsy severe rickets was present (Fig. 6).

Rickets. In 22 ribs (27%, excluding the two kwashiorkor cases mentioned above) significant histological evidence of rickets was found. In five cases the condition was severe. Our criteria of histological rickets corresponded approximately to those described by Follis.[4] It is possible, however, that we have not detected all very early cases, as we have found it difficult to distinguish between renewal of growth after growth depression, and early rickets.

The significance of the irregular capillary invasion of the epiphysis appears difficult to assess, especially in some kwashiorkor cases where capillary invasion is associated with depression of growth, as shown by the decreased width of the zone of proliferating cartilage. In view of the slight osteoid formation in some cases, this irregular invasion may be regarded as evidence of early acute rickets limited to this zone. On the other hand, it is possible to regard these changes as "normal" growth changes after a period of growth depression. In this paper these cases have not been included as rachitic, since growth depression was the predominant lesion.

Remaining Ribs. Of the 38 remaining Bantu infant ribs, in 15 (39%) the costochondral junction was essentially "normal." One rib showed well-marked congenital syphilitic lesions. The remaining 22 ribs (61%) showed evidence of growth depression, but to a much lesser extent than that found in kwashiorkor,

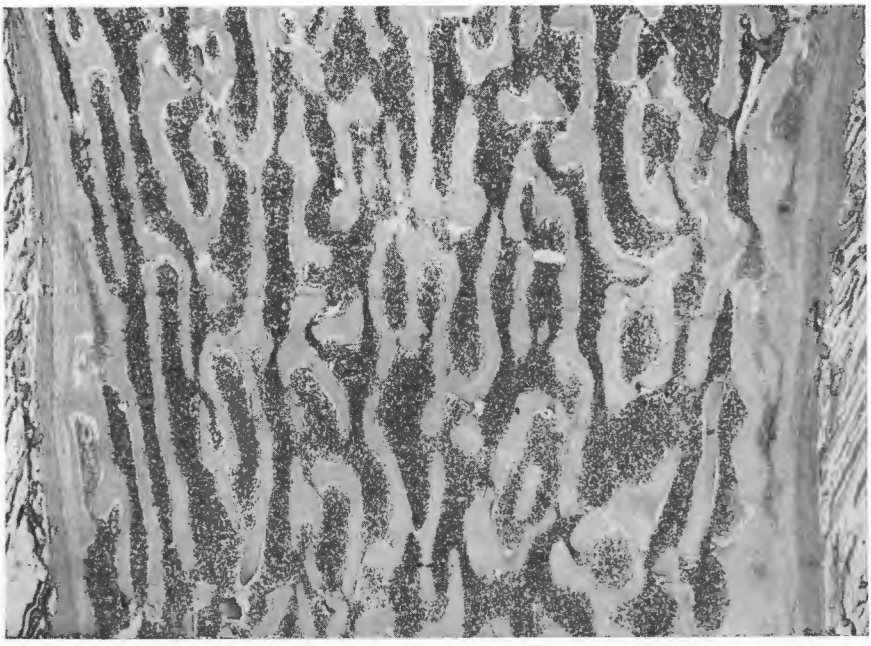

FIG. 5.—Shaft of fifth rib from moderately well-nourished infant dying from acute suppurative bronchopneumonia. Compare with Figure 4. Very slight rachitic changes were noted in costochondral junction. Bantu, female, 11 months. Mayer's hemalum and eosin, × 16.

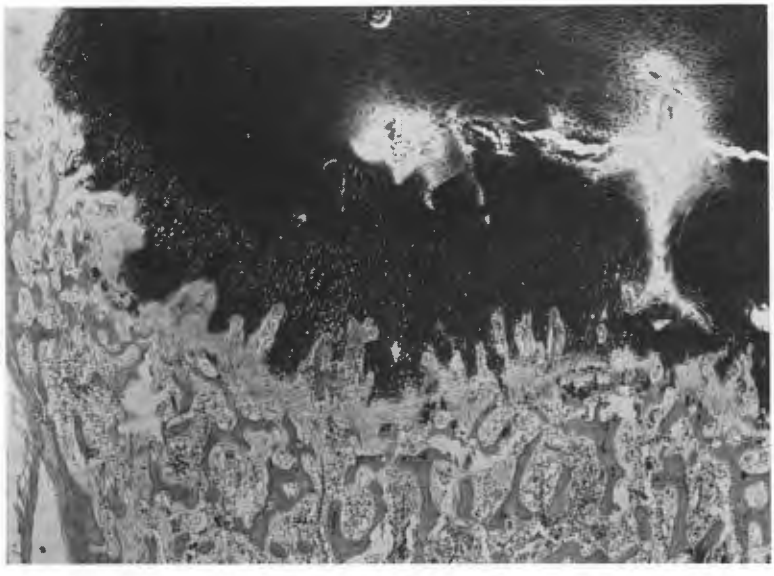

FIG. 6.—Moderate rickets in treated case of kwashiorkor after clinical improvement. Infant died suddenly from acute bronchopneumonia. Bantu, male, 14 months. Ehrlich's hematoxylin and eosin, × 20.

with the exception of two cases of gastroenteritis associated with severe malnutrition.

Children and Adults

Apart from some osteoid in the shaft of one Bantu child, aged 13 years, no significant lesion was observed in the ribs of 5 Bantu adolescents and 10 adults examined.

Discussion

In this series, growth depression was the most frequent lesion observed (52% of cases) and, as anticipated, was most marked in kwashiorkor, in which it was almost invariably present. The pathogenesis of this condition has not yet been elucidated, but undoubtedly both calorie and protein deficiencies are involved. Gillman and Gillman[5] have previously mentioned the depression of bone growth in three of seven kwashiorkor cases.

Comparable bone growth depression has been produced experimentally by subjecting animals to many different dietary deficiencies, including deficiencies of calories, proteins and vitamins. Silberberg and Silberberg[6] described in detail the bone changes in guinea pigs after periods of underfeeding. They found a decrease in the zone of endochondral ossification which was proportional to the degree and duration of underfeeding. The cartilage also became edematous, swollen and later sclerosed, and the cells atrophied and developed pyknotic nuclei. Edema and swelling of the intercellular stroma of the marrow was marked, but Harris's lines of arrested growth were not observed. The changes in the ribs of children dying from kwashiorkor thus parallel to some extent the lesions in these guinea pigs, but sclerosis of the cartilage was not observed and the marrow changes were less pronounced, both in the shaft and subepiphyseal zone. It is probable that the changes are essentially of the same nature but of different degree, being modified in the human by variations in the severity and duration of malnutrition.

Gillman and Gillman have described the generalized osteoporosis apparent on radiological examination of Bantu infants dying from kwashiorkor. Our observations provide histological confirmation for this finding, as illustrated in Figures 4 and 5, and suggest that the osteoporosis in these children is due to severe growth depression and atrophy, and not to increased osteoid formation in the shaft as in rickets. It is clear, therefore, that although the composition of bone is normal in most of these subjects, the total quantity of bone in the body is probably reduced.

Histological confirmation is also provided for the existence of rickets among urban Bantu children, despite the presence of plentiful sunshine. Unfortunately, on the rural population there is inadequate clinical and no histopathological data. It should be added that histopathological rickets is also common among American children. Follis and co-workers,[7] in their study on children up to 2 years of age, found the disease to be present in over half of a large series examined, the stigmata being moderate to severe in over two-thirds of the cases.

It has for long been observed that rickets will not develop during cessation of growth,[8] and this explains its absence in untreated and progressive kwashior-

kor. If, however, improvement occurs, growth recommences with irregular capillary invasion along the junction, and it is probable that in the absence of prophylactic treatment rickets will supervene, as in the case described.

Summary

In Part I of this study, the chemical composition of rib bone from Bantu subjects was found to be within normal limits, closely similar to that of European subjects.

The present study describes histological findings in a series of Bantu children dying in hospital. Observations have shown that, although bone composition is normal, this does not imply healthy growth or the absence of osteoporosis.

As anticipated, growth depression was the most frequent lesion observed, being most marked in cases of kwashiorkor. Histological evidence of rickets was found in 20 cases (25%).

Observations suggest that osteoporosis among these children is more likely to be the result of growth depression than of rickets.

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Studies on Human Bone from South African Bantu Subjects

I. Chemical Composition of Ribs from Subjects Habituated to a Diet Low in Calcium

By A. R. P. WALKER AND ULLA B. ARVIDSSON

IT IS widely believed that calcium absorption and bone calcification in man are controlled by the amounts of vitamin D, calcium and phytate phosphorus ingested, by the calcium/phosphorus ratio, and possibly by the amounts of protein and fat consumed.[1-4] The high cereal diet of the South African Bantu is low in vitamin D and calcium and high in phytate phosphorus and has an adverse calcium/phosphorus ratio (occasionally as wide as 1:10); it is probably adequate in calories and gross protein, but is low in fat.[5-10] The diet of these people, therefore, excluding that of breast-fed infants,[11, 12] is poor in calcifying capacity according to current views.[2, 4, 13-15] There is certainly plenty of sunlight, an average of eight hours per day in the Transvaal; but some authorities, such as Hess,[16] consider that a pigmented skin can promote the development of rickets by prejudicing the production of vitamin D from radiation.

To learn whether the type of diet consumed by these people affects the degree of mineralization of bone, we have determined the chemical composition of fifth ribs from a series of Bantu infants, children and adults. Part II of this study deals with the histopathological changes observed in these and other Bantu infants.[17]

MATERIALS AND METHODS

The proportions of ash, calcium and phosphorus were determined in fifth ribs from mainly consecutive necropsies of 44 Bantu infants, 13 children and 12 adults. Ribs from 18 European infants and 22 adults were also assayed for com-

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From the Human Biochemistry Unit of the South African Institute for Medical Research, Johannesburg, and the South African Council for Scientific and Industrial Research, Johannesburg, South Africa.

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TABLE 1.—*Percentage Composition of Dry Defatted Ribs**

Group	Race	No. of subjects	Ash	Calcium	Phosphorus
Infants†	Bantu (nonrachitic)	29	55.82 ± 2.4 (45.2–61.3)	22.65 ± 1.8 (17.3–27.7)	10.70 ± 0.8 (8.9–12.7)
	Bantu (mild rickets)	12	53.42 ± 3.8 (46.3–59.5)	21.66 ± 1.9 (18.1–24.4)	10.36 ± 0.7 (9.2–11.5)
	Bantu (severe rickets)	3	52.06 ± 2.4 (49.2–54.8)	20.46 ± 1.6 (18.5–24.3)	10.50 ± 0.5 (9.8–11.3)
	Bantu (severe malnutrition, kwashiorkor)	12	57.70 ± 1.8 (54.6–61.3)	22.85 ± 0.9 (20.6–27.7)	10.80 ± 0.7 (9.8–11.8)
	S. A. European	18	57.04 ± 2.9 (50.4–61.1)	22.24 ± 1.7 (19.6–25.9)	10.80 ± 0.6 (9.7–12.1)
Children‡	Bantu	13	56.70 ± 2.6 (51.4–60.2)	22.74 ± 1.1 (21.3–24.5)	10.53 ± 0.6 (9.6–11.5)
Adults	Bantu	12	57.10 ± 2.8 (53.1–63.5)	22.52 ± 1.3 (21.0–25.1)	10.44 ± 0.8 (8.9–12.1)
	S. A. European	22	55.67 ± 3.9 (45.9–60.0)	22.01 ± 1.5 (18.4–24.6)	10.67 ± 0.8 (8.3–11.5)

* It was found that preservation in 10% formalin did not affect analytical data.
† Up to 2 yrs., inclusive.
‡ Three to 15 yrs.

parison. Unfortunately, the ribs of five European infants and all adults were not, like all other ribs, preserved in 10% formalin, and were therefore not available for histopathological examination. All subjects died in hospital from disease, except the European adults who died from traumatic injuries. Duplicate analyses were carried out on samples (about 0.5 cm. long) removed just proximal to the costochondral junction. Adhering fat and muscle were cut away, and the pieces of bone were boiled in Bloor's mixture (ethanol 3 parts, ether 1 part) under reflux for 12 hours to extract all fatty matter. Marrow was also removed from a number of samples, using a dissecting needle, the freeing of this material being facilitated by a jet of water.[18] The bones were dried overnight at 110 C. Determination of ash, calcium and phosphorus were carried out by methods recommended by McCance and Shipp.[19] Occasionally, results were checked by methods described by Sobel, Rochenmayer and Kramer.[20]

Our results are summarized in Tables 1 and 2.

DISCUSSION

There is evidence that bones from different parts of the body differ slightly in chemical composition.[21, 22] This fact must be borne in mind in comparing our data (all carried out on fifth ribs) with those of overseas workers (Tables 3 and 4).

Observations on the ribs of infants will be discussed initially and in detail, since the changes attributable to diet are most likely to be demonstrable in actively growing bone.

TABLE 2.—*Percentage Composition of Dry Defatted and Demarrowed Ribs*

Group	Race	No. of subjects	Ash	Calcium	Phosphorus
Infants*	Bantu (nonrachitic)	8	59.9 ± 1.4 (57.0–62.2)	23.6 ± 0.7 (22.0–25.1)	11.30 ± 0.4 (10.6–11.9)
	Bantu (severe rickets)	3	43.7 ± 6.1 (31.1–50.7)	16.60 ± 2.6 (12.4–19.7)	8.16 ± 1.3 (5.8–9.6)
	Bantu (severe malnutrition, kwashiorkor)	5	60.3 ± 1.6 (58.4–62.2)	24.36 ± 0.5 (23.7–25.1)	11.38 ± 0.1 (11.0–11.7)
	S. A. European	4	58.25 ± 0.7 (57.1–59.4)	22.8 ± 0.9 (21.8–24.1)	10.90 ± 0.3 (10.3–11.7)
Children†	Bantu	5	59.5 ± 1.4 (58.0–62.1)	23.87 ± 0.6 (23.0–24.8)	11.42 ± 0.3 (11.0–11.9)
Adults	Bantu	7	61.9 ± 2.3 (58.8–64.7)	24.25 ± 1.0 (23.0–25.6)	11.70 ± 0.4 (10.3–12.3)
	S. A. European	17	59.6 ± 2.8 (54.6–64.1)	23.87 ± 1.0 (22.3–25.7)	11.07 ± 0.5 (10.4–12.0)

* Up to 2 yrs. inclusive.
† Three to 15 yrs.

Infants

In the dry defatted ribs of the Bantu and European subjects (Table 1), the ranges in the percentages of constituents show a wide distribution, but the ranges are less wide in the dry defatted and demarrowed ribs (Table 2). It is therefore apparent that the wide ranges in the non-demarrowed bones are due mainly to differences in the proportion of marrow present. Obviously, as Follis[18] has shown, data on demarrowed bones afford the truer reflection of degree of mineralization. However, since many of the earlier published studies were carried out on non-demarrowed bone, we have included our results for comparison (Table 3).

The differences between the concentrations of ash, calcium and phosphorus, respectively, in the demarrowed ribs of nonrachitic Bantu and of the European infants are not significant (Table 2).

Excluding the infants dying with rickets, we have discerned no correlation between nutritional state and the composition of bone. Of the 44 infants, 18 were still being breast fed before dying; yet the differences in bone composition between the breast-fed and weaned infants are not significant, so that separate data have not been given. Attention is drawn to the finding of normal composition of ribs of Bantu infants dying from severe malnutrition, kwashiorkor (Table 2).

Our observations contrast with those of Toverud and Toverud,[23] who reported the ribs of infants from well-nourished mothers to be better mineralized than from mothers who had consumed a less adequate diet during pregnancy (mean percentages of ash, 55.65 and 55.42, respectively; see Table 3). However, the ranges of values were not given, nor were their bones demarrowed.

In our small series of dried defatted and demarrowed bones examined, we

TABLE 3.—*South African Data on Dry Defatted Ribs Compared with Other Reported Data*

Group	Race	No. of subjects	Rib no.	Ash	Calcium		Phosphorus	
					Bone	Bone ash	Bone	Bone ash
Infants*	Bantu	29	5th	55.8	22.65	40.0	10.7	19.2
	S. A. European	18	5th	57.0	22.25	38.9	10.8	18.9
	Norwegian (well-fed mothers)[23]	26	7th	55.65		38.4		
	Norwegian (inadequately fed mothers)[23]	7	7th	55.42		37.9		
	American[34]	2	6th		22.58		10.84	
Children†	Bantu	13	5th	56.7	22.74	40.1	10.5	18.5
	American[34]	1	6th		21.96		10.27	
	American[18]	4	6th, 7th or 8th		22.82		10.78	
Adults	Bantu	12	5th	57.10	22.52	39.5	10.44	18.3
	S. A. European	22	5th	55.67	22.01	39.5	10.67	19.2
	German[35]		not stated			38.8		17.4
	German[36]		not stated			37.1		16.95
	American[34]	1	6th		22.20		10.11	
	American[18]	6	6th, 7th or 8th		23.2			
	American[21]	1	9th	57.54	22.2	39.0	9.55	16.6
	American[22]	1	10th	52.10	19.27	36.99	8.69	16.68

* Up to 2 yrs. inclusive.
† Three to 15 yrs.

found no significant difference between the percentages of constituents in the ribs from the Bantu nonrachitic infants and adults.

Turning now to the infants dying with rickets present; with the mild cases, the average ash and calcium figures are slightly reduced, but with the three severe cases, these figures are still further reduced (Table 2), owing probably to the presence of osteoid in the shaft. The question arises whether the pattern of diet common to the Bantu is responsible for this deficiency disease. In Johannesburg, rickets is common among urban Bantu infants.[24-26] Yet, Feldman[26] and Kahn[27] have observed that the majority of patients with rickets are *breast-fed* babies under 9 months. Lack of calcium is unlikely to be involved, since we have found the calcium concentration of 190 Bantu breast milk samples to lie within normal limits; moreover, the yield of milk is believed to be ample, at least for the first six months of lactation.[11, 12] It may also be pointed out that Ritchie[28] found the milk of Australian mothers with rachitic babies to be not essentially low in calcium. Feldman[26] and Kahn[27] have noted that, once Bantu infants are able to walk and move around by themselves, the incidence of rickets falls rapidly, being rarely seen after the age of 2 years. While a low intake of dietary vitamin D and inadequate exposure to the available radiation would

TABLE 4.—*South African Data on Dry, Defatted and Demarrowed Ribs Compared with Other Reported Data*

Group	Race	No. of subjects	Rib no.	Ash	Calcium	Phosphorus
Infants*	Bantu (nonrachitic)	8	5th	59.9	23.6	11.3
	S. A. European	4	5th	58.25	22.8	10.9
Children†	Bantu	5	5th	59.5	23.9	11.4
	American[18]	4	6th, 7th or 8th		25.11	11.5
	English[37]	11	5th		24.4	
Adults	Bantu	7	5th	61.9	24.3	11.7
	S. A. European	17	5th	59.6	23.9	11.1
	American[18]	6	6th, 7th or 8th		26.1	11.8
	English[37]	9	5th		25.6	

* Up to 2 yrs. inclusive.
† Three to 15 yrs.

appear to be the primary cause of rickets among urban Bantu infants, it is probable that other factors are involved, as Follis[29] has concluded in relation to the commonness of histological rickets found among American young children.

Children

Our data on the ribs of Bantu children differ very little from the figures given for American and English children (Tables 3 and 4).

Adults

Our findings reveal a close similarity in the respective mineralization figures for Bantu adult subjects, South African European, also American and German adult subjects (Tables 3 and 4). Our observations support the conclusion of Nicholls and Nimalasuriya,[30] who found there was very little difference between the percentage of calcium in bones (tibia and femur) from European and from Singalese subjects, the latter being habituated to a diet similar to that consumed by the Bantu (i.e., low in calcium, etc.).

The constancy of composition of human ribs from subjects of different races dwelling in different regions and accustomed to diets of different pattern, demonstrates that the calcium content and the calcium/phosphorus ratio of the diets consumed have very little influence on the percentage composition of bone. Furthermore, it may be pointed out that, even under conditions of severe undernutrition and starvation, Keys and co-workers,[31] from a review of the literature, have concluded the concomitant effect on bone composition to be slight.

Our results on humans confirm conclusions reached from studies on rats,[32] namely, that level of calcium intake, within limits, does not affect percentage of calcium in bone. It must be emphasized, however, that our data refer exclusively to *percentage composition*, and provide no information on the proportions of *mineral constituents per kilogram of body weight*. It is certain that on the

latter basis there are differences, as are indicated by the photographs of sections of Bantu bone given in Part II of this study.[17] On the other hand, it must be pointed out that there is no evidence, either from the Bantu population or from prisoners of war subjected to prolonged gross calcium deprivation,[33] that such differences are of practical importance in so far as liability to fractures or rate of healing of fractures are concerned.

Summary

The South African Bantu are habituated to a diet low in calcium and vitamin D, high in phytate phosphorus, and with an adverse calcium/phosphorus ratio. According to many authors, such a diet would be expected to influence the degree of mineralization of their bones.

To investigate this problem, assays of ash, calcium and phosphorus have been made on the dry defatted (and occasionally demarrowed) fifth ribs of Bantu infants, children and adults, and of European infants and adults. No significant difference has been found between the percentage composition of (*a*) infant ribs from both races and (*b*) adult ribs from both races. All data are in close agreement with reported values for white subjects dwelling both in South Africa and in Western countries.

It is concluded that, under local climatic conditions (including plentiful sunlight), the dark skin of the Bantu does not prevent formation of bone having normal mineral composition, nor does the supposedly poor calcifying diet, even that consumed by weaned infants dying from severe malnutrition (kwashiorkor). Our results thus confirm conclusions reached from studies on rats, namely, that the level of calcium intake, within limits, does not affect the percentage composition of bone.

The low mineralization figures found in some infants (mainly breast fed) dying with rickets, are judged to arise mainly from inadequate intake of vitamin D and insufficient exposure to the available radiation.

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THE COMPOSITION AND DENSITY OF THORACIC VERTEBRAL BODIES FROM SOUTH AFRICAN BANTU ADULTS HABITUATED TO A VERY HIGH IRON INTAKE

A. R. P. WALKER, E. S. P. STRYDOM, P. A. REYNOLDS AND B. G. GROBBELAAR

Human Biochemistry Research Unit of the South African Institute for Medical Research, Johannesburg, and the South African Council for Scientific and Industrial Research; and Department of Pathology, Baragwanath Non-European Hospital, Johannesburg

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The iron intake of the South African Bantu is unusually high, as much as 200 mg. *per diem*; such iron is largely adventitious and derived from utensils used in food preparation; the uptake of the element is particularly marked with the traditional fermented cereal foods (pH 2—3), which are consumed very frequently in large amounts.[1] At necropsy abnormal deposition of iron (or siderosis) is apparent in the tissues of more than half the urban adults examined;[2, 3, 4] there are high concentrations in the spleen, liver, jejunum and bone marrow, but not in the pancreas and heart; this distribution differs distinctly from that observed in classical haemochromatosis and transfusional siderosis.[4] Values for serum iron and total iron-binding capacity are frequently elevated, and occasionally are higher than corresponding values in the 2 diseases just mentioned; saturation of the serum is not observed.[5, 6] Hypochromic anaemia is less common than would be expected from the nutritional and parasitic conditions prevailing.[7]

In a previous paper, which dealt with the morbid anatomical distribution of the siderosis, attention was drawn to the commonness of haemosiderin-containing macrophages in sternal marrow smears from adult patients.[4] Recently one of us (B.G.G.), in the course of an unpublished study[8] of 110 consecutive necropsies of adult Bantu, found 2 cases of collapse of lumbar vertebrae. In these patients the vertebral bodies showed intense brown colouration which, on histological examination, was found to be due to heavy deposition of haemosiderin. There was no evidence of replacement of fibrous tissue in the collapsed vertebrae. In these and in other severely siderotic bodies microscopic examination revealed haemosiderin in both fixed and free macrophages of the bone marrow, extracellular deposits also being noted occasionally. There were no haemosiderin granules present in the bone trabeculae. Severely siderotic bodies showed evidence suggestive of bone atrophy and diminished

osteoclastic activity. The osteoporosis was particularly marked in the 2 patients with collapsed vertebrae.

The precise aetiology of the osteoporosis and collapse of the vetrebrae as seen in the Bantu is still obscure and is being investigated at this hospital. Thus Grusin[9] has noted that osteoporosis and scurvy are frequently seen together in the same patient. He has also found osteoporosis and collapse in comparatively young patients (as young as 34 years), which indicates that senility is not a major aetiological factor. Siderosis is so common in the Bantu that it was decided to investigate its role in the aetiology on the osteoporosis. To throw light on this issue we have determined the concentrations of iron and also of ash and calcium, and the mineral density, of vertebral bodies from a series of consecutive necropsies of Bantu adults; also of European adults to serve as controls. Such information should reveal whether intensity of siderosis can be correlated with bone composition and density.

MATERIALS AND METHODS

Material

The vertebral bodies from mainly the 5th, though occasionally the 6th and 7th, thoracic vertebrae were removed at consecutive necropsies of 77 adults, comprising 47 men and 30 women. Ages ranged from 20 to 73 years, the mean age being 43 years. Subjects included 2 males aged 51 and 54 years with collapsed vertebrae, which were osteoporotic according to both radiological and histo-pathological assessments. All subjects came from areas where previous studies had shown habitual intake of iron to be high.

For controls, vertebral bodies from the 5th thoracic vertebrae were obtained from consecutive necropsies of 11 European adults, comprising 7 men and 4 women. Ages ranged from 34 to 88 years, the mean age being 66 years.

In no case was the primary cause of death related to the presence or absence of siderosis or osteoporosis.

Methods

Chemical analysis. For chemical analysis, segments of the vertebral bodies, and occasionally the total bodies, were taken. To facilitate removal of material adhering to the bone, samples were boiled in water for 2 hours. The material was cut away by means of stainless-steel forceps, scissors and scalpel. The last traces were removed by erosion with a garnet sandpaper attached to a plane circular rotating surface. Samples were finally dried overnight in a hot-air oven at 90-95° C and then weighed. Ashing was carried out, also overnight, at 450°-550° C. After moistening the ash with a few drops of glass-distilled water, 5 ml. of iron-free concentrated HCl were added, and samples were covered with a watch-glass and left until

solution was effected. This took anything from a few minutes to 3 days. The solution, after boiling and diluting with water, was filtered; the basin was washed twice with N/2 HCl, and the extracts bulked to 100 ml. Iron was determined by the thioglycollic-acid method,[10] and ash and calcium as described by McCance, Widdowson and Shackleton.[11]

Density determinations. Mineral matter per unit volume of vertebral body was estimated as follows: First the volume of the vertebral body was determined. For this purpose a wide-mouthed weighing bottle, 2 inches in diameter and 2 inches deep, was placed in a 6-inch Petri dish on a plane surface. The vessel was carefully filled with mercury, by means of a burette, to the point of just overflowing, the slight overflow being removed with a capillary pipette. The vertebral body, held by thin-pointed forceps, was slowly and with the utmost care, submerged in the mercury, and as carefully withdrawn. The displaced mercury was weighed and, its density being known, viz., 13·55 at 20° C, its volume was calculated, this figure being equal to the volume of the displacing body. Vertebral bodies which permitted significant penetration of mercury were excluded from density-measurement studies. Duplicate determinations agreed to within 1%. Correction was made for the volume of the points of the forceps introduced into the mercury. To check the accuracy of the method, the volume of various small bodies (lumps of various ores, pitch, plastics, etc.) were determined by the mercury-displacement method and then by the Archimedes method (weighing in air and then in water with appropriate corrections). Values were found to agree within 5%. From the volume of the vertebral body and the weight of the ash on ignition, the mineral matter per unit volume of body could be calculated.

The density of the bone ash was determined as follows: A 10-ml. specific-gravity bottle was weighed, filled with chloroform at 20° C and weighed again, and the volume occupied by the chloroform calculated (density of chloroform at 20° C is 1·49). Vertebral-body ash was introduced and weighed. The vessel, with frequent swirling, was slowly filled with chloroform at 20° C, and weighed again. From the weight of the added chloroform, and hence its volume, the volume occupied by the ash, and hence its density, could be calculated. Results on duplicate determinations agreed to within 1%.

De-marrowed vertebral bodies. Marrow was carefully removed from a number of opened vertebral bodies by means of a dissecting needle. Marrow was also removed from other opened bodies by the extraction method described by Williams and Irvine,[12] i.e., with a constantly boiling mixture (118° C at sea level) of aqueous (80%) ethylene diamine in a Soxhlet extractor.

RESULTS

Tables I—III give data of percentage mineral composition and other

data for the vertebral bodies of Bantu and European subjects. Tables IV and V summarize the data of mineral density.

In view of the range of iron-concentration found in European vertebral bodies, siderosis in the Bantu was regarded as *absent or slight* with values up to 100 mg. Fe% dry weight; *moderate* at 100—1,000 mg. Fe%; and *severe* if exceeding 1,000 mg. Fe%.

TABLE I. PERCENTAGE MINERALIZATION DATA OF VERTEBRAL BODIES OF BANTU AND EUROPEAN GROUPS OF SUBJECTS

(Means, standard deviations, and ranges)

Group of Subjects	*No. of Subjects*	*Age (years)*	*Iron (mg.%)*	*Ash (g.%)*	*Calcium (g.%)*
European	11	66·0±18·4 (34—88)	33·4±14·0 (18·6—66·4)	33·0± 7·1 (24·4—46·1)	11·6± 4·5 (8·7—16·1)
Bantu—siderosis absent or mild, < 100 mg. Fe%	34	38·4±16·7 (16—72)	43·5±16·6 (21·4—72·0)	40·7± 5·4 (31·3—50·6)	15·5± 2·2 (11·2—20·2)
Bantu—siderosis moderate, 100—1,000 mg. Fe%	31	46·0±15·7 (26—73)	433±272 (114—992)	41·9± 4·2 (35·7—48·9)	15·8± 2·3 (11·4—22·0)
Bantu—siderosis severe, > 1,000 mg. Fe%	12	44·5±10·2 (20—56)	1430±381 (1008—4009)	38·9± 4·8 (30·1—44·8)	15·7± 1·7 (12·0—17·8)

TABLE II. REPRESENTATIVE MINERALIZATION DATA ON ADJACENT THORACIC VERTEBRAL BODIES IN BANTU AND EUROPEAN SUBJECTS

Subject	*Position of Vertebra*	*Age (years)*	*Iron (mg.%)*	*Ash (g.%)*	*Calcium (g.%)*
European	5	72	22·1	31·0	11·7
	6		35·9	30·0	11·2
Bantu with no siderosis	5	72	43·9	50·6	21·1
	6		33·9	51·4	19·4
Bantu with severe siderosis	5	56	1021·0	46·2	17·3
	6		1126·0	46·8	16·4

TABLE III. MINERALIZATION DATA ON VERTEBRAL BODIES OF BANTU SUBJECTS DYING WITH COLLAPSED VERTEBRAE

Subject	*Position of Vertebral Body*	*Age (years)*	*Iron (mg.%)*	*Ash (g.%)*	*Calcium (g.%)*
Bantu male	Collapsed lumbar vertebra	51	1,103	32·9	—
	5th thoracic vertebra		1,298	30·1	13·7
Bantu male	Collapsed lumbar vertebra	54	1,923	41·6	19·4
	5th thoracic vertebra		4,009	36·1	16·9

TABLE IV. MINERAL DENSITY DATA ON BANTU AND EUROPEAN VERTEBRAL BODIES
(Means and ranges)

Subjects	*No. of Subjects*	*Iron (mg./ml.)*	*Ash (g./ml.)*	*Calcium (g./ml.)*
European	8	0·2 (0·1—0·4)	0·17 (0·15—0·20)	0·055 (0·03—0·07)
Bantu. Siderosis absent or slight	11	0·2 (0·1—0·4)	0·21 (0·14—0·24)	0·08 (0·05—0·09)
Bantu. Siderosis moderate or severe	13	4·3 (0·7—8·6)	0·18 (0·14—0·24)	0·075 (0·05—0·09)

TABLE V. MINERAL DENSITY DATA ON VERTEBRAL BODY BONE ASH FROM BANTU AND EUROPEAN SUBJECTS
(Mean values and ranges)

Subjects		*No. of Subjects*	*Iron (mg./ml. bone ash)*	*Ash (g./ml. bone ash)*	*Calcium (g./ml. bone ash)*
European		9	3·1 (1·8—6·7)	2·95 (2·86—3·10)	1·01 (0·66—1·31)
Bantu	Siderosis absent or slight	8	4·1 (2·1—7·2)	2·98 (2·83—3·09)	1·21 (0·89—1·44)
	Siderosis moderate or severe	9	95 (11·4—200)	2·99 (2·81—3·11)	1·19 (0·91—1·43)

The extent of the leaching-out of the iron by the 10% formalin was found to be insignificant; even with the intensely siderotic bodies the iron concentration in the formalin did not exceed 3·2 mg. Fe per 100 ml. Next, the increase in the iron concentration in the water used for boiling the bodies to facilitate the removal of cartilage was also very small—not exceeding 0·8 mg. per 100 ml. The iron concentration in the cartilage did not exceed 5·3 mg. Fe per 100 g. in the Europeans; in Bantu in whom siderosis was absent or mild, the figure varied from 19·5 to 44·0 mg. Fe but in the presence of intense siderosis the amount varied from 55·5 to 102·8 mg. Fe per 100 g. of dry cartilage material. Hence the presence of small traces of cartilage adhering to vertebral bodies is unlikely to affect the chemical data to any significant extent.

DISCUSSION

Information on the iron concentration in human bone, whether cancellous or compact, from any part of the body is extremely meagre. In a recent review on the storage of elements in the skeleton, Duckworth and Hill[13] dealt with the concentration of 36 different elements, but iron was not mentioned. Even before the present century, German workers had noted the large number of diseases in which some measure of siderosis was

apparent at necropsy. Thus in 1882 Peters (quoted from Hunter[14]) listed no less than 30 diseases. It is therefore surprising that at present, well over half a century later, extremely little is known of the iron concentration of vertebral bodies of subjects, whether in health, or suffering from diseases such as classical haemochromatosis, transfusional siderosis, pernicious and haemolytic anaemias, and so forth.

The occurrence of several extremely high iron-concentrations in the Bantu vertebral bodies examined (Table I) reaching 120 times the mean concentration in the European vertebral bodies, is noteworthy. In a previous study it was found that in the presence of intense Bantu siderosis the hepatic and splenic iron-concentrations reached as much as 50 and 80 times respectively the concentration in non-siderotic vertebral bodies.

It will be observed that the ranges of mineralization data (ash and calcium) in both Europeans and Bantu bodies are wide (Table I). The means for ash and calcium concentrations in the 3 Bantu groups (Table I) are closely similar and it is clear that there is no correlation between such concentrations and the severity of the siderosis as reflected by the mean iron-concentrations. On a mean percentage weight basis, the European vertebral bodies contain a significantly higher proportion of organic matter than do the Bantu bodies ($P < 0{\cdot}05$). In the bone ash the mean percentages of calcium are: in the Bantu group with siderosis absent or slight, 38·1% Ca; with moderate siderosis, 37·7% Ca; with severe siderosis, 40·4% Ca; and in the European group, 35·2% Ca. The mean value for the 77 Bantu bodies is 38·8% Ca. The mean calcium-concentration in the bone ash of the Bantu vertebral bodies is not significantly higher than the mean for the Europeans. Incidentally in a previous investigation[15] we found the mean percentage of calcium in the bone ash of 5th ribs of 12 Bantu adult and 22 Europeans to be identical, namely, 39·5%.

In Table II representative data are given for adjacent vertebral bodies from European and Bantu subjects. Data are similar, although not identical. In view of the self-contained character (speaking relatively) of the vertebral bodies, such differences are not unexpected. Moreover, with other bony tissues there is evidence that the composition differs from bone to bone within the same body;[16, 17] even in the same rib, differences in chemical composition have been noted throughout the length of the bone.[18]

Turning now to our mineral density data on bone and bone ash (Tables IV and V), we find that the mean mineral matter per unit volume of European vertebral bodies is almost identical with the mean of the Bantu group with moderate and severe siderosis. The mean value for the European group is significantly less than that for the Bantu group among whom siderosis is absent or mild ($P < 0{\cdot}05$). Several of the siderotic bodies had a density value of less than the mean; on the other hand

this was not always the case. There is thus no clear-cut correlation between mineral density data and the severity of siderosis. Incidentally, we wish to emphasize the finding of satisfactory mineral density in the vertebral bodies of the Bantu, who are habituated to a calcium intake far less than the allowances usually recommended. In osteoporosis, the bone trabeculae are fewer and thinner, while the interstitial spaces are larger; hence, although a given *weight* of osteoporotic bone has the same mineral composition as a like weight of normal bone, a given *volume* of osteoporotic bone would weigh less than its counterpart of normal bone. In the severely siderotic bodies, were osteoporosis or bone atrophy marked, it would be expected to be manifested in the density data, i.e., mineral matter per unit volume of body. In the present series, this figure in the European bodies varied from 0·15 to 0·20, and in the Bantu bodies from 0·14 to 0·24; no clear-cut correlation was apparent.

The correlation of severe siderosis and osteoporosis in the vertebral bodies assessed histologically, and the lack of correlation between iron concentrations and mineral density data, is probably an apparent rather than a real disagreement. Firstly, it will be evident that a marked reduction in mineral density (possibly attributable to siderosis) could occur without necessarily depressing the figure below the normal range. Secondly, the vertebral bodies on which density determinations were made did not include, unfortunately, those of the 2 patients dying with collapsed vertebrae; moreover, since collapse occurs only at 1 or 2 points, it would be incorrect to assume that the mineralization of any one vertebral body is representative of the mineral density of the spinal column.

To pursue the density aspect further, horizontal macro-sections about 1/10 inch thick were taken from vertebral bodies representative of each group, shaken in alcohol, dried, and examined by naked eye. It was not possible to satisfactorily pick out which were (1) European bodies, (2) Bantu bodies with slight siderosis, and (3) Bantu bodies with severe siderosis. Further, samples of vertebral body from which marrow had been extracted were examined under a dissecting microscope by Dr. A. G. Oettle of this Institute; observations regarding mesh, regularity and trabeculae revealed slight, though not invariable, differences between the groups. No bone, including those classified as severely siderotic, could be regarded as atrophic, and all observations were in harmony with the respective mineral density data.

We wish to emphasize that our knowledge of the whole subject of osteoporosis and mineralization is far from satisfactory. For example, in regard to radiological assessment, Baker and associate workers[19] took X-ray pictures of a series of slices of different thicknesses of the cortex of bovine femurs; they found that under the conditions of clinical radiology it required at least 50% increase in calcium content to give any clearly visible differences in radiological density. Babaiantz[20] found that

when human vertebral bodies were slowly de-mineralized with dilute nitric acid, and X-rayed at regular intervals, 30% of the calcium had to be removed before the loss was apparent radiologically, and 50% before the body could be described as osteoporotic. Obviously, clarification of this subject will be possible only when a large series of relevant subjects are examined radiologically before death, with subsequent studies on the histo-pathology, composition and density of the vertebral bodies. Table V shows that the mean density of *bone ash* from the vertebral bodies of all groups is the same; there is thus no correlation between bone-ash density and siderosis.

In a previous paper it was concluded that there is no evidence that excessively high iron stores arising from oral iron 'overload' are detrimental to well-being, although the possibility that pathological lesions might ultimately occur could not be excluded. In classical haemochromatosis, where extremely heavy deposits of iron are usual, Sheldon[21] considered that some obscure disturbance of calcium metabolism is present; although, in his more recent contribution, X-rays are reported to reveal no abnormality.[22] No reports have been found of osteoporosis occurring characteristically in transfusional siderosis, pernicious anaemia, or other diseases marked by abnormal iron deposition, although the subject appears to have been little investigated. It would thus seem that siderosis *per se* does not cause an osteoporosis. In the present series of 80 consecutive Bantu adults examined at post-mortem, there were 2 cases of collapsed vertebra, yet very severe siderosis was noted in 12 vertebral bodies. Collapse of the vertebrae thus occurred in only 1 out of 6 adults with very severe siderosis. While, therefore, it appears certain that siderosis is not the major aetiological factor in the type of osteoporosis and collapse of the vertebrae under discussion, its role as a promotive factor clearly requires further study. It is planned to investigate the problem more intensively when a large series of vertebral bodies from patients dying with collapse ultimately become available.

SUMMARY

Abnormal deposition of iron in various tissues is noted in about one-half of urban Bantu adults examined at necropsy, the siderosis being attributable primarily to habitual excessively high intake of iron.

Generalized osteoporosis with collapse of lumbar vertebrae has been observed in a small number of Bantu subjects, whose bone marrow revealed intense deposition of haemosiderin. In addition, a degree of bone atrophy has been noted in sections of severely siderotic vertebral bodies. In view of the association of collapse and osteoporosis with siderosis, the possible causative role of the latter has been investigated.

A series of thoracic vertebral bodies has been studied from consecutive necropsies of Bantu adults, and of European adults as controls. Our

findings indicate: (1) Extremely high concentrations of iron are common; 15% of bodies from consecutive subjects had concentrations exceeding 1% of iron in dry weight, i.e., about 30 times the normal proportion present. (2) There appears to be no clear-cut correlation between iron concentration, and ash and calcium concentrations, reckoned on either *percentage* or *volume* basis, i.e., severe siderosis is not necessarily associated with low mineral density.

It is suggested that siderosis is not the major causal factor in the collapse and osteoporosis of the vertebrae occasionally seen in the adult Bantu; as a promotive factor, however, the role of siderosis merits further investigation.

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THE SIGNIFICANCE OF LOW SERUM CALCIUM VALUES IN THE SOUTH AFRICAN BANTU

A.R.P. WALKER, M.Sc., PH.D., ULLA B. ARVIDSSON, B.Sc.

Human Biochemistry Unit of the South African Institute for Medical Research, Johannesburg, and South African Council for Scientific and Industrial Research

and

W. M. POLITZER, M.D.

Biochemical Department, South African Institute for Medical Research, Johannesburg

According to accepted standards, the diet of the South African Bantu, in common with that of many indigenous peoples dwelling in tropical and semitropical countries, is markedly deficient in calcium[1-6]. Moreover, as we have mentioned elsewhere,[7] the dietary intake of vitamin D is negligible, that of phytate phosphorus is high, the calcium-phosphorus ratio is adverse (occasionally as wide as 1 : 10), and the intakes of protein and fat are less than are usual among White communities. These dietary factors are listed by many authorities, for example Bicknell and Prescott,[8] as being unfavourable for the absorption of calcium. There is, of course, plenty of sunlight (an average of 9 hours per diem in the Transvaal) although some authorities like Hess[9] consider that a dark skin militates against the production of vitamin D from radiation. According to current views, stigmata of calcium deficiency should be apparent, and low levels of the element in the blood serum have been listed by some investigators.[10, 11] That low levels are common among Natives of Southern Africa, who are habituated to a low intake of calcium, is borne out by local evidence.[12, 13] Nevertheless, the view that low serum calcium values are evidence of calcium deficiency, and of reduced body stores, etc., is of questionable validity and open to a number of criticisms which will be discussed in this paper.

For a number of years at this centre we have been interested in the subject of calcium metabolism under conditions of low intake, and consequently we have determined serum calcium values on children and adults as opportunity offered. Particular attention has been given to pregnant and multiparous long-lactating mothers, among whom the effects of the drain of the element on serum values are of obvious interest.

We wish to stress that our studies concern Bantu children and adults in outward good health, and that subjects with altered serum calcium concentrations arising from various metabolic disorders, including rickets, have been excluded. The metabolism of calcium in the latter disease will be discussed in another paper.

SUBJECTS AND METHODS

(1) *Boys.* (*a*) 23 subjects, aged 7-12 years, were out-patients at Coronation Non-European Hospital, Johannesburg, suffering from cuts, minor burns, and other ailments not likely to influence serum calcium levels. (*b*) A further group of 54 boys, aged 14-15 years, were delinquents at Diepkloof Reformatory, Johannesburg. They had been detained there for some months, and were employed on farm lands producing food (including milk) for their own consumption.

(2) *Adult Males.* 48 men, aged 18-40 years, were newcomers from different Southern African territories examined in Johannesburg and passed as medically fit for service on the gold mines.

(3) *Adult Females.* The 33 adult women were either out-patients or newly-admitted in-patients at Baragwanath Non-European Hospital, Johannesburg, suffering from ailments unlikely to affect their serum calcium levels.

(4) *Pregnant Women.* The 38 subjects examined were out-patients in their last trimester attending either Baragwanath Hospital, or a peri-urban health centre (Mooiplaats) near Pretoria, for routine examination. Medical officers considered their state of health to be representative of urban Bantu pregnant women.

(5) *Lactating Women.* The 55 subjects studied were either patients in Baragwanath Hospital admitted on occasions when their babies required treatment, or were out-patients attending that hospital or the peri-urban health centre mentioned previously. The mothers selected and studied were considered to be representative. Subjects had had 2 or more children, and had fed their babies for at least 5 months up to 12 months, the babies deriving all or almost all their nourishment from the breast milk.

Blood samples were taken by venipuncture, usually about 11 a.m. Serum calcium was determined by the method of Tisdall and Kramer as modified by Clark and Collip.[14]

The results are summarized in Table I. For comparison, data on other groups of subjects are included.

TABLE I.—SERUM CALCIUM VALUES IN BANTU AND OTHER GROUPS

Group	Subjects	No.	Serum Calcium (mg. %) Range	Mean
1. Boys	(*a*) Bantu (Coronation)	23	8·8—11·8	9·9± 0·8
	(*b*) Bantu (Diepkloof)	54	9·2—12·6	10·3± 0·9
	Kikuya [13]	5	10·0—10·6	10·3
	Belgian Congo [16]	10		10·1
	American [15]	85	10·0—11·5	10·9
2. Adult Males	Bantu (Southern Africa)	48	7·9—10·9	9·5± 0·7
	Bechuanas [13]	42	7·8—11·2	9·5
	Kikuya [12]	90	7·3—11·4	9·4
	Indian [17]	10	8·2— 9·4	9·0
	Indian (students) [18]	25	9·4—12·4	10·85
	Indonesians [19]	17	8·8—11·7	10·0
	American Negroes [20]	309	9·0—11·85	10·4
	Irish (working class) [21]	19	10·0—10·9	10·3
	Irish (students) [21]	130	9·5—12·9	11·0
3. Adult Females	Bantu (S. Transvaal)	33	7·6—11·1	9·3± 0·8
	American [22]	16	9·7—11·3	10·4
	American [23]	207	10·0—11·5	10·8
4. Pregnant Women (7-9 months)	Bantu (S. Transvaal)	38	8·9—11·3	9·9± 0·7
	Indian [24]	20	9·0—10·5	9·8
	American [22]	33	8·7—10·8	9·5
	American [23]	900		9·9
	British [25]	96	6·0—13·7	9·35
5. Lactating Mothers	Bantu (S. Transvaal)	55	9·3—12·8	10·2± 1·0

DISCUSSION

It will be apparent that our results on Group 1a boys and on our adult males and females, groups 2 and 3, confirm the findings of other local workers,[12,13] namely that mean serum calcium values in the Bantu are roughly one-tenth lower than the figures for the corresponding groups of White subjects cited.

The initial question is whether these low values are compatible with good outward health, or whether they are essentially pathological and likely to be associated with relevant clinical stigmata. The Porto Rican soldiers studied by Ashford and Hernandez,[26] the Bechuana Bantu investigated by Squires,[13] and also the Bantu mine-workers studied by us, all were in good outward health; moreover, the last group was passed as medically fit for hard physical work. Yet both Squires' subjects and our own were drawn from populations known to have been habituated to a calcium intake considerably less than that common among Europeans. The first point then is that low serum calcium values are common and that they occur in apparently healthy hard-working people.

If low values are not pathognomonic *per se*, what is their significance, i.e. what do they indicate or measure? The following 2 points are relevant:

(1) It has been observed that subjects habituated to a low calcium intake, and who have low serum calcium levels, may have the latter raised by improvements in diet. Thus, a group of Chinese mothers in poor nutritional condition had an average serum calcium value of 8.6 mg.%; after consuming the hospital diet the value became 9.3 mg.%.[27] The Indian repatriated prisoners-of-war studied by Walters *et al.*[28] had an average serum calcium value of 8.6 mg.%; on hospitalization this was raised to 10.2 mg.%. The Central African patients of Orr and Gilks [12] had an average value of 9.3 mg.% before entering hospital; after treatment (for tropical ulcer) the mean value became 10.5 mg.%. Further, although our data on the Bantu boys in Groups 1a and 1b are not strictly comparable, it is probable that the higher mean value for the boys from Diepkloof Reformatory was due to their consumption of a diet of superior nutritional value compared with the diet of the out-patient boys living in Coronationville. The rise in values in the examples described may have been due either to the consumption of a more nourishing diet (more protein, etc.), or to the ingestion of a higher calcium intake, or to both causes.

(2) With White subjects, investigation has shown that administration of calcium supplements can slightly elevate serum calcium levels.[29-31] The elevations occur within 2 hours after ingestion of the supplementary calcium; further, the elevations appear to be transitory, lasting for a few hours only and returning to previous levels once the supplements are no longer given. The rapidity of elevation and fall suggests that serum calcium levels are unrelated to extent of body stores; also, it may be inferred that the elevations described in the previous paragraph were due to increases in calcium intake rather than to other changes in diet.

Briefly then, it would seem reasonable to consider that low mean serum calcium values in population-groups probably reflect habitually low intakes of the element, and do not essentially indicate low body stores.

Serum calcium in pregnant Bantu women. In White women it is a common observation that as pregnancy progresses serum calcium concentration falls, but returns to its previous level after parturition.[32] If serum calcium concentration in the Bantu responds to pregnancy in the same way in White women, then, assuming the groups to be comparable, one would expect the mean concentration for the group at term to be *lower* than the mean value for the non-pregnant group. Our Table, however, indicates an apparent *rise* during the pregnancy of Bantu women; moreover, the value at term approximates to that for the groups of White mothers mentioned.

Serum calcium in multiparous long-lactating Bantu mothers. An average White mother has a total body-calcium of approximately 900-1,100g.[33] During pregnancy, she provides the foetus with 20-30g. calcium,[33] and if she feeds her baby exclusively by breast feeding for 6 months, she loses an average of 60 g. calcium.[34] For the Bantu, neither the total calcium in the mother nor the amount of the element in the foetus has yet been determined. The drain of calcium from the breast milk, however, is known to be similar to that for White mothers.[35,36] It will be apparent, therefore, that lactation, especially prolonged lactation as is usual among the Bantu, constitutes a much greater demand for the element than occurs during pregnancy. It is interesting therefore that the mean serum calcium concentration for our 55 multiparous long-lactating mothers was found to be higher than the mean value in the non-pregnant state and also higher than the mean value at term. Unfortunately, no corresponding data for long-lactating White mothers have been reported. Our findings are in harmony with the absence of reports of the occurrence of osteomalacia in pregnant and lactating Bantu women, despite their being accustomed to a diet of low calcium content. To throw additional light on the subject it is our intention to determine serum calcium values from early pregnancy until late in lactation in *the same individual Bantu women.* To obtain such data will obviously take a considerable time, and it has been thought worth while to publish such information as we have already secured.

While it is apparent that good health may be enjoyed despite low serum calcium levels, it may be of interest to enquire whether the latter predispose to certain conditions, for example low calcium concentration in breast milk, inferior mineralization of bone, proneness to fracture of bones, and increased incidence of dental caries.

Calcium concentration in Bantu breast milk. Since milk is isotonic with blood, and milk calcium is derived from blood calcium, the question arises whether the low serum calcium values sometimes, though infrequently, observed in lactating Bantu mothers (Group 5) prejudice the calcium concentration of the breast milk. Firstly, the calcium concentration of Bantu milk, as alluded to above, has been found to vary within wide limits, [35,36] yet no wider than those limits and with the same average value that have been reported for American [34] and British [37] mothers' milks. Next, our detailed observations have revealed no correlation between serum calcium and breast-milk calcium values in the same mother. Observations on cows have shown that in the presence of low calcium intake and depleted calcium reserves, milk of normal calcium concentration is produced, but the yield is reduced. [38,39] Local paediatricians, however, maintain that Bantu mothers almost invariably have a good yield of milk, and aver that for the first 6 months there is parity in growth and general health between European and Bantu babies when exclusively breast fed. This information suggests, therefore, that low calcium intake and occasionally low values in the serum prejudice neither the calcium concentration in the breast milk, nor the total yield of milk.

Mineralization of bone. In Ceylon, the general calcium intake is low,[40] but unfortunately no serum calcium data are available. However, Nicholls and Nimalasuriya[40] found the mineral composition of various bones from Singalese subjects to be the same as for European subjects who had been resident and had died in Ceylon. We have carried out a similar though more extensive study in this country, reaching the same conclusion.[41] Low serum values are therefore compatible with normal composition of bone.

Proneness to fracture of bones. Even though bone composition be normal it is conceivable that a low calcium intake and low serum calcium levels may reduce the *total* amount of bone laid down, thereby reducing tensile strength and predisposing to fractures. There appears to be no evidence that this is the case, in so far as fractures are concerned, for the view has been expressed that even with gross deprivation of calcium and other nutrients, adequate trauma is necessary to cause fractures.[42,43] But exact data of this type on the Bantu, or indeed on any other population, are not easy to obtain. Indirect evidence is available from the ¼ million Bantu mine-workers employed on the Witwatersrand; for senior medical officers consider that these Natives, who are accustomed to hard and sustained physical work, are no more liable to fracture their bones than are Europeans. It is also considered that when fractures occur in the Bantu, callus formation is more extensive and rate of healing more rapid than are observed with Europeans suffering from corresponding injuries. While these impressions are not decisive, they suggest that low serum calcium values *per se*, correlate neither with a high incidence of fractures nor with a delayed rate of healing.

Proneness to dental caries. Many authors believe that a low intake of calcium militates against satisfactory dentition and promotes dental decay. A corresponding claim does not appear to have been made in respect of low serum calcium values. It may be added that evidence from this country,[44, 45] Bechuanaland,[46] Southern Rhodesia,[47] and Central African territories,[48] indicates that the general incidence of dental decay among the Bantu is lower than among Europeans.

SUMMARY

Serum calcium values have been determined in groups of Bantu children and adults in good outward health. It has been found that, in common with other populations

dwelling in tropical and semitropical countries, low serum calcium values are frequently observed.

Discussion of our results and other relevant information indicates the following: (1) Low serum calcium values are compatible with good outward health. (2) The values probably reflect habituation to a relatively low intake of calcium. (3) They do not provide an indication of the extent of stores of body calcium. (4) They do not predispose to (*a*) low concentration of calcium in the breast milk; (*b*) poor mineralization of bone; (*c*) proneness to fracture bones, or (*d*) an increased incidence of dental caries.

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Does a Low Intake of Calcium Cause or Promote the Development of Rickets?

By A. R. P. WALKER, M.SC., PH.D.*

THE PRESENT position regarding the requirement of calcium and the signs of its deficiency is far from satisfactory. This is evident from recent publications. Thus, Hegsted and co-workers[1,2] have noted that the recommended allowances of calcium are based largely on balance observations, the uncertainties of interpretation of which are well known. Goldsmith,[3] moreover, has reiterated Macy's contention of ten years ago, namely, that "neither the most satisfactory level of calcium intake nor the optimal retention of calcium at any physiologic age or stage of man's development is known."

A high intake of the element is often recommended on the grounds that a low intake causes or predisposes to the development of rickets.[4–10] But it is noteworthy that standard textbooks on pediatrics, in the main, do not appear to regard level of calcium intake of much significance.[11–13] Moreover, other authorities reject the implication of calcium deficiency in the etiology of the disease, maintaining that it does not occur provided adequate vitamin D be present (excluding vitamin D-resistant rickets).[11,14,15] In view, first, of the differences of opinion on the subject, and second, its relevance to recommended calcium allowances, it has been thought desirable to examine the literature and seek to learn to what extent calcium is involved in the etiology of the disease. The conclusion reached in this paper is that there is no specific evidence that a low calcium intake promotes, still less causes rickets, such findings thereby increasing misgivings on current views on calcium requirement and deficiency.

The first point to be appreciated is that there are a large number of factors which militate against a precise evaluation of the role of calcium intake in rickets.†

FACTORS WHICH MILITATE AGAINST SATISFACTORILY ASSESSING THE ROLE OF CALCIUM DEFICIENCY IN THE ETIOLOGY OF RICKETS

(1) *Uncertainties in Diagnosis*

There are four types of diagnostic criteria: clinical, radiological, histo-pathological, and chemical analysis of bone.

(a) *Clinical Assessment.* Among pediatricians, there is no dispute as to the signs of severe rickets. But the same unanimity of opinion is absent over mild rickets, the clinical signs of which Park[16] stated to be "notoriously deceiving and cannot be relied upon."

(b) *Radiological Assessment.* The previous statement likewise applies to diagnosis from roentgenograms. It must be stressed that the radiological picture associated with poorly mineralized bone can arise from many causes and, as Youmans[17] has pointed out, too often osteoporosis has been uncritically interpreted as the result of lack of calcium. Furthermore, the poor measure of agreement between clinical and radiological assessments of rickets deserves emphasis. In the British Pediatric Survey,[18] which was carried out in 1942 by a panel of specialist workers, the clinicians confirmed positive radiological opinion in less than half the cases of rickets;

From the Human Biochemistry Unit, South African Institute for Medical Research, Johannesburg, and South African Council for Scientific and Industrial Research.

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* Head of Human Biochemistry Unit.

† Throughout this paper *clinical* rickets is in mind unless otherwise stated.

conversely, the radiologists confirmed positive clinical opinion in one out of twenty-five cases.

(c) *Histo-pathological Assessment.* Here, the assessment is based on microscopic examination of a section of the costo-chondral junction of the rib. Unfortunately, however, there are differences in grading adopted by different groups of workers. In the comprehensive studies of Follis and co-workers,[19,20] histologic rickets was stated to be present in over half of the large series of American children examined at necropsy, severe rickets being present in about two-thirds of the cases. Were the same standard of critical judgment used for non-American children (usually in a less privileged nutritional condition), the proportion graded as *free* from rickets would be very small indeed, in which case the condition could be regarded as of normal or even of physiological occurrence.

(d) *Chemical Analysis of Bone.* Very few studies on the composition of human bone in rickets have been carried out, as is evidenced by Hawk *et al.*[21] citing German studies exclusively, which were published over forty years ago. A recent investigation has been carried out by this Unit on the chemical composition and histological appearance of the fifth rib of South African Bantu infants, children, and adults (also European controls). In mild rickets, it was found that mineralization data (ash, calcium, and phosphorus) lay within the same range as for non-rachitic subjects; only in severe rickets (graded clinically and histologically) were reduced values found.[22,23] Unless the rachitic lesions be severe, therefore, chemical analysis of bone appears to be of little diagnostic value.

In view of the above difficulties, it would simplify the position if all four criteria for rickets could be used on the same patients. But since histological and chemical studies can be undertaken only on post-mortem material, and since it is very rare among Western peoples for young children to die with severe clinical rickets, such an investigation could be carried out only with the greatest difficulty.

(*2*) *Limitations of Studies on Children*

The only reliable method of determining the relationship between the occurrence and severity of rickets, and the habitual level of calcium intake, would be to induce rickets in young children on diets low only in calcium, and then to observe the effect on the lesions of appropriate additions of calcium salts. To deliberately induce rickets in children is, of course, out of the question. As Mackay[24] succinctly observed at a symposium on diseases of infancy held in London, "How many members would offer their babies as experimental animals for a study of the infants' requirements of this or that nutrient?"

In regard to therapeutic investigation, if deficiency of the element *is* implicated in rickets, then at least some ameliorating effect should be demonstrable with calcium supplements only. But in order satisfactorily to demonstrate and assess this therapeutic effect, several difficulties will be met. First, as already indicated, the position relating to the assessment of the severity of rickets is unsatisfactory. Uncertainties would therefore be present not only in choosing a comparable group of patients to be studied, but in assessing the progress made; in the British Pediatric Survey[18] referred to, there were frequent differences of opinion over the presence of "active" and "healed" rickets. Next, it would be essential to know the calcium status of patients. But as Darby,[25] also Goldsmith,[3] have noted, there is no present method of determining calcium status, i.e. calcium stores, and past and present calcium intakes. Finally, regarding treatment, difficulties involved in keeping, not only the diet, but the degree of exposure to radiation carefully controlled for protracted periods, will be appreciated. Unless all variables are kept to a minimum, clear-cut conclusions cannot be drawn.

The difficulties described thus show some of the obstacles which must be overcome before the rôle of calcium intake in rickets can be evaluated.

Quite apart from the uncertainties outlined, inherent in such an investigation, no study appears to have been made in which

the response to calcium has been compared with the response to vitamin D, or calcium plus vitamin D. Such a study was not included in the classical investigation of rickets in Vienna in 1919–1922,[26] possibly because the usual hospital diet, which was shown to have no healing effect on children with rickets, was already rich in calcium. That severe rickets can occur in the presence of ample calcium has, of course, been observed from early times.[6,12,26–30] The fact that the remedial effect of calcium has not been demonstrated satisfactorily does not, however, prove that a supplement of calcium has *no* effect on rickets. But in view of the large amount of interest taken in the etiology of rickets by able authorities of the past, Cheadle,[27] Findley,[28] Mellanby,[6] Hess,[11] Park,[29] and others, it would seem reasonable to consider that whatever healing effect is engendered by the addition of calcium only can be of little clinical significance.

Calcium Intake and Rickets in Populations and Population Groups

It is widely held that the requirement of vitamin D is influenced, *inter alia*, by the amount of calcium ingested; i.e., a high calcium intake requires less vitamin D to facilitate its absorption compared with a low intake, and vice versa.[31,32] In other words, some vitamin D can spare some calcium. However, as Jeans[33] has stressed, with decreasing calcium intake, vitamin D cannot compensate indefinitely, for a point must be reached where, even if all the calcium ingested were absorbed, the amount absorbed would be insufficient for satisfactory bone formation. But the critical level may well be lower than is generally imagined, for equilibrium and good retentions are known to occur at low levels of intake.[34–39] This is attained, first, by absorbing a greater percentage of calcium, and second, by reducing the amount excreted; i.e., retentions can be comparable to those obtaining with higher levels of intake.

What happens, then, to the incidence of rickets when the calcium intake is lowered, as often occurs in wartime, or, when it is habitually low? These two states will be considered separately.

The Incidence of Rickets among Populations whose Calcium Intake has been reduced

It must be constantly kept in mind that rickets is a disease of *growing* bone, for among children whose growth is retarded or arrested, rickets is not observed.[4,6,26–29] Now all diets which support growth *must* contain a modicum of calcium. If calcium intake be decreased, what point is reached first? Is it the point where insufficiency of the element causes bone to be poorly mineralized, or, is it the point where the concomitant lack of other nutrients (calories, proteins, etc.) causes a slowing down of growth, thereby automatically arresting the development of rickets? Were the former alternative valid, rickets would be a characteristic feature of undernutrition. But this is not so. Reviewing wartime experience as a whole, Keys *et al.*[40] have concluded that there was no increase in the incidence of rickets. Furthermore, under conditions where all nutrients were often severely restricted, as at Belsen,[40,41] Warsaw,[42] starving Holland in 1945,[43] and in the Japanese prisoner of war camps,[44] rickets was not observed. Evidently the diets consumed either had sufficient calcium available for satisfactory bone growth, or, before the level of calcium became too low, lack of other nutrients arrested bone formation and rickets did not supervene. It is apparent, therefore, that the belief that progressive lowering of calcium intake causes or promotes the development of rickets is not supported by wartime experience.

The Incidence of Rickets among Populations whose Calcium Intake is habitually low

Populations may be divided into two groups: (1) those dwelling in the tropics and semitropics, where the intake of calcium is habitually low, but where available radiation is plentiful; and (2) those dwelling in northerly countries where the calcium intake is higher, but where available radiation is less plentiful.

(1) Populations where Calcium Intake is low but Radiation plentiful.

In several regions in the tropics and semi-tropics, for example, East Africa,[45] Rhodesia,[46] Indonesia,[47] Burma,[48] and rural India,[49,50] although the habitual calcium intake is almost invariably low, clinical rickets is believed to be rare. In South Africa, in both rural and urban areas, such rickets is rare among the school child[51–53] and the younger population.[54] However, in crowded centers of population, in South Africa,[55–57] as well as in India,[49–50] rickets is common and occasionally severe. In Johannesburg, for example, rickets is frequently observed, but the majority of the patients are breast-fed Bantu babies whose intake of calcium is normal. After two years, when the child begins to move around and fend for itself, rickets is rarely seen, although at that time the child's calcium intake (in proportion to its accepted requirement) is at its lowest throughout the life period.[56,57] Gillman and Gillman[58] have noted their astonishment that gross bone deformity is not more widely prevalent in older Bantu children.

Concerning adult rickets or osteomalacia, no case of this disease in a pregnant Bantu woman has yet been reported from Central or Southern Africa. The disease is common in India,[50] though apparently only among women who practice purdah (seclusion). It is of interest to note that there is evidence that the poorest of Chinese women who are forced throughout the season to work in the fields do not get osteomalacia, despite the consumption of a most unsatisfactory diet characterized by its low calcium content.[59–61] Among Chinese women on a slightly higher social plane, and who can afford to remain indoors, particularly throughout the inclement winter, osteomalacia is common. There appears to be no evidence, therefore, that a low calcium intake causes or promotes the development of osteomalacia.

(2) Population Groups among whom Calcium Intake is higher, but available Radiation is less plentiful.

Unfortunately, no investigation on the incidence of rickets occurring exclusively among low consumers of calcium has been carried out. There are, however, a number of studies which suggest indirectly that the level of calcium intake is of little relevance in the disease. A few examples will be given. Glasgow is situated in latitude 58°; moreover, being an industrial city, reduction of ultraviolet radiation by smoke and smog must occur to an appreciable extent. In this city, one of the most comprehensive studies on rickets was carried out by Findlay and Ferguson in 1919.[62] A salient finding was that although the diet consumed by the non-rachitic children was only slightly superior to that of the rachitic subjects, of the latter, 40 per cent were not taken out regularly, while only 4 per cent of the non-rachitic children had been confined indoors regularly. More recently, Rustung[63] carried out a study of rickets incidence still further north in an inland Norwegian valley. The incidence of the disease was high, particularly up to school age (30–40 per cent). The diet was composed mainly of cereals and vegetables, with a variable though usually a small amount of milk. Rustung found that freedom from rickets was closely associated with the length of time the children spent in the open air.

Furthermore, the frequently observed and sometimes dramatic effect of season on the incidence of rickets, despite probable constancy of calcium intake, is pertinent. For example, in a study in wartime Denmark, Fredericia[64] reported that the incidence of rickets in the first year of life was 22 per cent in the spring, but only 1.4 per cent in the summer and autumn.

The examples given, while not demonstrating calcium intake to be of no importance, at least suggest that level of calcium intake has little etiological significance.

Briefly, then, the evidence on the population groups discussed here, although it is admittedly inadequate, provide no support for the belief that the level of calcium intake is an etiological factor in the development of rickets.

Comment

It will be apparent from what has been discussed that a low calcium intake *per se* does not *cause* rickets. It is possible that low consumers of calcium are more susceptible to vitamin D deficiency than are high consumers of the element: i.e., for an equal vitamin D deficiency, a subject habituated to a low calcium intake may develop rickets earlier and more severely than a subject used to a higher intake. But there appears to be no evidence in favor of this possibility. Certainly, among the reasons advocated for a high level of calcium intake (and no dietary standards body has yet adduced detailed clinical and pathological evidence in support of this), it would be unwarrantable to include prophylaxis against a deficiency disease whose relationship to calcium deficiency is so far from being established. It would be equally unwarrantable, as the writer has shown elsewhere, to recommend a high calcium intake to guard against the inhibiting effect of phytate phosphorus on the absorption of calcium,[65] to ensure adequate mineralization of bone,[22] or to safeguard against retardation of growth or stuntedness at maturity.[66]

In the light of the foregoing, it is submitted that the time is opportune for a re-examination of the whole position relating to calcium requirement and deficiency stigmata.

Summary

It is widely believed that a low intake of calcium can cause or predispose to the development of rickets.

To determine accurately the responsibility borne by a low level of calcium intake in the etiology of rickets is almost impossible, due to (1) the unfeasibility of carrying out a carefully controlled study, (2) uncertainties in the diagnosis of the disease, and (3) lack of a reliable method of assessing the calcium status of patients.

If calcium deficiency be implicated, calcium salts should evoke some ameliorating response. Such an effect has not been satisfactorily demonstrated.

Wartime experience has indicated that when calcium intake is reduced, even drastically, no increase in the incidence of rickets occurs. In tropical and semitropical countries where a low calcium intake is almost invariable, rickets is uncommon when advantage is taken of the available radiation. In countries less favored in the latter respect, no studies on rickets appear to implicate, even indirectly, the level of calcium intake as an influencing factor.

While there seems to be no evidence that a low calcium intake promotes, still less causes, rickets, the possibility that level of intake has a modicum of etiological significance cannot be completely excluded. It would seem wholly unwarrantable, however, to list prophylaxis against rickets as a reason for insisting on the high intakes of calcium at present recommended.

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THE EFFECT OF ENVIRONMENTAL CONTEXT ON AGEING.

It is often thought that many of the stigmata seen in middle aged and old people are either due to, or are promoted by the process of ageing. This view, however, is one which requires constant re-appraisal as newer knowledge becomes available on populations in different parts of the world. The result is that many conditions or diseased states common in the West are found to be imposed, not essentially by ageing, but by particular contexts of environment, and possibly by the operation of an ethnic factor.

In considering this subject, it is imperative, of course, to allow for the differences in age structure which are found almost invariably in contrasting populations. In the United States, expectation of life has risen from about 50 years at the turn of the century to almost 70 years at the present time;[1] in 1900, 4 per cent of the population were 65 years or older; by 1960, the proportion of such people had risen to 9 per cent.[1] Among a somewhat primitive and underdeveloped population, however, such as the South African Bantu, present expectation is not known but certainly it is less than 50 years, this lower figure being due primarily to the still high mortality rate prevailing among the very young. The proportion of urban Bantu aged 65 years and over is about 1.5 - 2.0 per cent.[2] Accordingly, for the above reason alone, crude prevalences of certain degenerative diseases or other stigmata associated with ageing are far higher in privileged compared with less privileged communities. Comparisons of the health situations in different populations are meaningful only when data relate to corresponding age groups.

A few of the conditions or diseased states often linked with the ageing process will now be discussed.

WEIGHT: Formerly, gain in weight with age among adults was thought to be unavoidable. But this is not the case with various primitive or relatively indigent populations, e.g. poor Indians,[3] African Samburu[4] and Bushmen.[5] In the United States, it has been estimated that one fifth of the population over age 30 (about 15 million persons) may be considered overweight (i.e. 10 per cent above "ideal" weight); about 10 per cent is obese (15 per cent over "ideal"weight); finally, about 5.5. million (approximately 3 per cent) are pathologically obese (20 per cent above "ideal" weight).[6] The hazards to health and expectation of life from this cause are well documented.

BLOOD-PRESSURE: Among White populations blood pressure rises with age. In some Non-White populations, e.g. U.S.A. Negroes, the rate of increase with age is much greater than that of Whites.[7] Yet among a number of primitive or indigent populations, e.g. poor Indians,[3] African Samburu[4] and Bushmen,[5] certain Australasian[8] and South American populations,[9] and Gilbertese,[10] blood pressure does not rise with age. The handicap to health imposed by hypertension is well established; in particular, there is increased liability to die from hypertensive heart disease, cerebral vascular disease, coronary heart disease, and diabetes.

SERUM CHOLESTEROL CONCENTRATION: Among White populations and prosperous Non-White populations, it is usual for serum cholesterol and other blood lipid components to rise with age. Yet only a slight rise or even no rise with age has been

reported to occur among many underprivileged Non-White populations, e.g. poor Indians,[3] rural Japanese,[11] and certain groups of South African Bantu.[12] Among populations who have habitually low serum cholesterol levels, the severer sequelae of atheroscleroses are seldom seen, and deaths from coronary heart disease are rare.

ARTERIAL DEGENERATION: Numerous studies have been carried out on the pathologic changes in arteries with age. Certain degenerative changes arise and develop, even in foetuses;[13] but the severe changes often seen in the arteries of the privileged in late youth, middle and old age, are not physiological.[14] Fatty streaks appear to be ubiquitous in man, yet ulceration and calcification, are not. In ~~certain~~ less privileged populations, the calcium concentration of aorta changes only slightly with age; in ~~others~~ more favoured populations, the concentration increases considerably.[14,15] Furthermore, in some populations, the thickness of the wall of the aorta or coronary vessels in adults changes little; in privileged populations the thickness may increase three fold with age.[16,17]

CORONARY HEART DISEASE: In most Western populations this disease is the leading cause of death of adults. In New York, the disease accounts for about a third of all deaths in the 47 - 74 years period.[18] In Johannesburg, South Africa, the figure for Whites is closely similar;[19] in Johannesburg Jews, the proportion is higher.[20] Among underprivileged populations the relevant mortality rate (age specific) often is far lower.[14,16,17] Deaths from the disease remain rare among the South African Bantu, even, inexplicably, among the sophisticated moiety pursuing lives in many respects similar to those of Whites.[19,20]

GLUCOSE TOLERANCE ABNORMALITY AND DIABETES: In Western populations, glycosuria, glucose tolerance abnormality, and diabetes are common. But they are less common or even rare among certain populations, e.g. Alaskan Eskimos,[21] and the indigenous population of Papua and New Guinea.[22] Locally, among 400 indigent Bantu "pensioners" in Johannesburg, aged 60 - 100 years (average age 67 years), we found 1 hour post prandial glycosuria present in 6 subjects (1.5 per cent); and hyperglycaemia (2 hours post-prandial capillary blood "true" glucose, exceeding 120 mg. per cent) in 2 subjects (0.5 per cent.) The corresponding proportions of these conditions found in the diabetes study at Bedford, England, were approximately 9 and 5 per cent, respectively.[23] In a younger Bantu population, namely, ~~45~~ 50 school teachers, 45 - 60 years old, we found glucose tolerance glycosuria and "diabetic abnormality" in 4.0 and 0.0 per cent respectively.[24] In the Birmingham diabetes study, 14.5 per cent of the population over 50 years showed "diabetic abnormality".[25] It is clear from these figures that glucose tolerance abnormality of the intensity and frequency seen in elderly White populations, is not an accompaniment of ageing per se.

OSTEOPOROSIS: Osteoporosis (post-menopausal and senile) is a very common skeletal disorder during the middle and old age of Whites. In U.S.A., one report indicates there to be some 4 million sufferers with severe vertebral lesions.[26] The condition, however, appears to be seen far less commonly in U.S.A. Negroes,[27] or in the Bantu, in spite of their low calcium intake, which, in mothers, is exacerbated by the heavy drain of the element from numberous pregnancies and long lactations.[28] Osteoporosis, then, cannot be regarded as a phenomenon associated

with ageing per se.

COMMENT.

From the illustrations given it will be apparent that many of the conditions and diseases affecting the middle-aged and elderly in Western and other sophisticated populations, either occur less commonly or scarcely at all in under-privileged populations accustomed to a primitive, frugal, or simple manner of life.

One important question which arises is, - what can be done by Western populations to attain some of the enviable aspects of the physiologic picture of the primitive and under-privileged, yet without losing any of the commendable features of their own health picture? Conversely, what can be done by underprivileged populations to reduce their often high mortality from deficiency diseases and infections, without losing, directly or indirectly, any of the commendable aspects of their own health picture? Almost innumerable investigations are being undertaken in many parts of the world whose objects of research lie within the compass of these questions. Among Western populations, the impact of enlightenment, in respect of attempts to ameliorate the conditions and diseases referred to, has been slight. In regard of the less-privileged populations, such as the Bantu, while morbidity and mortality rates from deficiency and infectious diseases are falling, the prevalences of overweight and hypertension, stemming from the availability of plenteous calories and the urbanized way of life, are rising rapidly.[29] It would seem a forlorn hope to seek to engender the milieu in which the best health aspects of each way of life may be retained, because, speaking generally, they are incompatible and cannot co-exist in a

free society. Only at times when dietary and other changes are involuntarily imposed, as in certain European countries during and after World War II, may widespread beneficial changes ensue. In some of the countries affected, it was reported that obesity became less prevalent,[30] coronary atherosclerosis became less marked,[31] limited evidence suggests that deaths from coronary heart disease may have decreased,[32] and deaths from diabetes fell.[33] Yet once the conditions of privation were removed, the prevalences of these diseases and conditions rose even higher than the previous peace-time levels.

The subject under discussion is one which has exercised man down through the centuries. For those who lived righteously, there was the promise, "with long life will I satisfy him".[34] The search for the "Elixer of Life" by alchemists was costly in fortunes and in life long labour. At the present time there is no doubt that despite sustained endeavours, our knowledge of the minimal pathological sequelae of ageing is still very defective.[17,35-37] Only in non-sophisticated rural populations of the type described, accustomed to a settled and traditional manner of existence, will it be possible to attempt to arrive at the definition of the changes, - clinical, metabolic, and pathological, which arise specifically from ageing. There are a number of isolated communities in different parts of the world, not in nutritional want, yet not exposed to plenty, who fulfil these conditions, and who would therefore be suitable for the intensive and long-term prospective studies which are required.

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ALEXANDER R.P. WALKER, PH.D.
SOUTH AFRICAN INSTITUTE FOR MEDICAL RESEARCH,
JOHANNESBURG, SOUTH AFRICA.

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Chemical and Pathological Studies on Aortic Atherosclerosis

A Comparative Study of One Hundred Twenty-Eight Aortas in South African Bantu and White Subjects

M. ANDERSON, B.Sc.; A. R. P. WALKER, Ph.D.; W. LUTZ, D.Sc., and JOHN HIGGINSON, M.R.C.P., Johannesburg, South Africa

Introduction

The rarity of myocardial infarction among the hospitalized South African Bantu has made them a suitable community for studying the geographical pathology of atherosclerosis and coronary heart disease. It is generally accepted that myocardial infarction is rare in the Bantu,[1-4] but there is less certainty regarding the incidence of severe atherosclerosis. While atherosclerosis is widespread, it has been reported that in the older age groups severe atherosclerosis is less frequent than in Denmark and North America,[1,4] but this has recently been denied by Laurie and Woods.[5]

Since our earlier observations on the severity of atherosclerosis were subjective, we have attempted to determine whether these racial differences could be demonstrated more objectively by chemical analysis. Earlier studies, especially on the lipid fractions, indicated the feasibility of doing so in population groups, if not in individuals.[6,7] At the same time it was hoped that further information would be obtained on the value of this method in grading.

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Present address (Dr. Higginson): Department of Pathology and Oncology, University of Kansas Medical Center, Kansas City 12, Kan.

Human Biochemistry Research Unit (Miss Anderson). South African Institute for Medical Research, Johannesburg, and Council for Scientific and Industrial Research (Dr. Walker). Department of Mathematics, University of Witwatersrand (Dr. Lutz). Department of Pathology, South African Institute for Medical Research, Johannesburg (Dr. Higginson).

Accordingly, the dry weight, ash, and calcium, total fat, cholesterol, phospholipid, total nitrogen, elastin, collagen, and hexosamine concentrations were determined in aortas from Bantu and white subjects. While the extent of our study was limited and our series is small, it appears worth recording, since our findings indicate that racial differences in the chemical composition of the aorta do exist. They also cast some light on the value of these methods as a means of objective grading of atherosclerosis.

Materials and Methods

Source of Aortas.—The aortas from Bantu subjects were obtained from consecutive autopsies at Baragwanath Hospital, and those from white subjects, at the Johannesburg General Hospital. To increase numbers in certain age groups poorly represented in the hospital material, unselected aortas were also obtained from the Medico-Legal Laboratories in Johannesburg. All aortas were unselected except that cases of syphilitic aortitis were excluded. Altogether, 70 aortas from Bantu subjects and 58 from white subjects were available for study.

The unfixed aortas reached the laboratory within four hours of removal from cadavers. They were then graded and photographed. After stripping the adventitia and trimming, blocks for histology were taken through the severest lesions in the arch and descending and abdominal portions. This also permitted a check on the adequate removal of the tunica adventitia.

A. Chemical Analysis

The aortas were cut up into portions about 0.5 cm. square and dried for 24 hours approximately in a vacuum desiccator over concentrated sulfuric

acid. This procedure removed all but about 5% moisture, the residual figure being determined on a separate small sample of tissue dried to constant weight at 100 C. The vacuum-dried material was ground in a Willey Mill, using 20-mesh sieve, and stored in airtight receptacles in a cool place.

Ash and Calcium.—Ash and calcium were determined as described by McCance and Shipp.[8]

Total Lipid.—From 200-400 mg. of dry tissue was extracted with Bloor's mixture (alcohol-ether, 8:3) for 10 hours in a Soxhlet apparatus. The solvent was removed and the lipids extracted with petroleum ether (petroleum benzin), at 60-80 C. The latter was evaporated off, and lipids were dried to constant weight at 70-80 C. Duplicate analyses agreed to within 2%.

Phospholipid.—The method of King[9] was employed. Duplicates agreed within 1%.

Cholesterol.—From 50-100 mg. of tissue was digested for about three hours with 0.2 NaOH. The mixture was extracted three to four times with alcohol-acetone (1:1). The supernatant liquors were decanted off and made up to volume (25-100 ml.). Cholesterol was determined by the Liebermann-Burchardt color reaction, as described by King.[9] Duplicate analyses agreed to within 3%.

Total Nitrogen.—This constituent was determined by a micro-Kjeldahl method, as described by Pregl.[10]

Collagen and Elastin.—One hundred milligrams of tissue was defatted with 100 ml. of alcohol-acetone (1:1). The supernatant was removed by decantation and autoclaved with 5 ml. of distilled water in 20 ml. test tubes with raw cotton (cotton wool) for three hours at 25 lb. pressure. This procedure was repeated three times. The supernatant fluids were then poured off, pooled, dried in an air oven at 80 C, and evaporated to dryness. This operation converts the collagen to gelatin but leaves the elastin undissolved. Both elastin and gelatin fractions were hydrolyzed separately with 2 ml. of 6 N HCl for six hours at 25 lb. pressure. Hydrolysates were neutralized with 6 N NaOH, filtered, and bulked (usually to 25 ml.). The amounts of elastin and collagen were determined by liberation of hydroxyproline, as described by Neuman and Logan,[11] the conversion factors being 7.46 for collagen and 52.3 for elastin. Ox hide, highly purified (95% collagen), was used as a control and hydrolyzed simultaneously with each batch of samples. Recoveries varied between 96% and 101%. Duplicate analysis showed agreement within 5% for collagen and 7% for elastin.

Hexosamine.—From 30-50 mg. of tissue was hydrolyzed with 4 N HCl for 15 hours in glass-stoppered flasks (25 ml.). Hydrolysates were treated with Dowex-50 resin (an ion-exchange resin), as described by Boas,[12] to separate off amino acids and sugars, which interfere with the color reaction. After elution of the hexosamines, the color was developed by the method of Elson Morgan, as modified by Boas.[12] Destruction of added glucosamine during hydrolysis averaged 6.2%. Mean recovery of glucosamine standard treated with the resin was 90.4%. All results are presented as percentages of dry weight.

B. Grading of Atherosclerotic Lesions

The aortas were divided into four segments, and each was graded on naked-eye appearance according to the degree of atherosclerosis by one worker (J. H.), wholly unaware of the results of the chemical analysis, as follows:

0: No lesion (histological section, however, often showing slight intimal lesions in such cases)
1: Minimal scattered lesions, linear or patchy, whether fatty, mucinous, or fibrous
2: More advanced lesions with definite plaque formation
3: Plaques large and confluent and covering greater part of intimal surface, palpation and section sometimes showing slight calcification in such cases not visible to the naked eye
4: Definite ulceration and/or calcification; widespread involvement of the intimal surface usually present
5: The severest degree of atheroma with marked ulceration and calcification (arteritis deformans)

The values for all segments were summated, and a final grading of 0 to 5 was adopted. Representative aortas for each grade are shown in Figure 1.

This grading is subjective, and we would now prefer to use the more satisfactory classification proposed by Gore and Tejada.[13] Furthermore, since the aortas were destroyed in the chemical analysis, grading could not be carried out simultaneously, although comparison of photographs did permit some check (admittedly inferior) on the consistency of our grading. We consider that in future studies the vessel should be bisected longitudinally and only one-half used for chemical analysis, the other being retained for later grading. Further, it would have been preferable to have analyzed each segment separately, so that errors introduced by the summation of segments with wide variations could have been avoided. This error may partly explain the wide variation shown in some components. Finally, colored photographs would have been preferable to black-and-white prints.

Results

Effect of Sampling Errors.—Apart from subjective grading, the major source of inaccuracy in making comparisons between

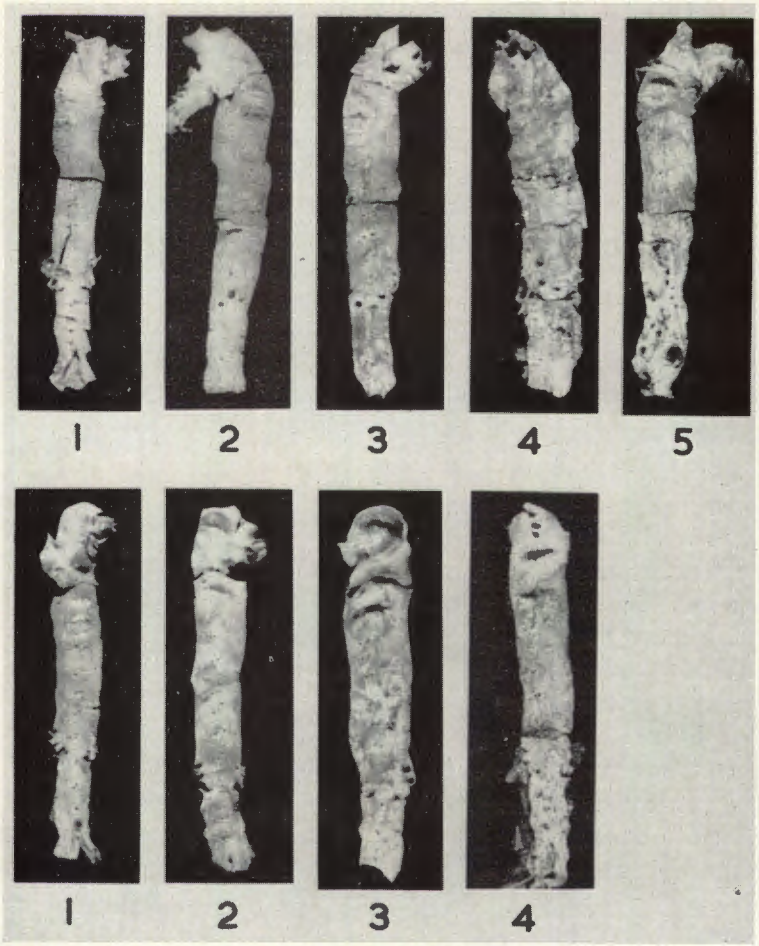

Fig. 1.—Composite photograph showing typical aortas in each grade from both races. The vessels from white subjects are in the upper group; the aortas from Bantu subjects are in the lower group.

Bantu and white subjects is a failure to use completely comparable samples from the two populations. Although we believe that our samples are free from intentional bias in regard to atherosclerosis, our numbers are small, and this possibility cannot be excluded with certainty. Despite these inadequacies, the differences demonstrated in certain chemical components are of sufficient magnitude and constancy as not to be readily explainable by sampling error, and almost certainly represent true differences between the two races. Moreover, the similarities in other chemical components support this view.

All statistical remarks are subject to the basic assumption that the autopsies are a random and representative sample of both the Bantu and the white populations. The calculations have been made according to methods given by Hald.[14] Unless stated otherwise, the term "significant" is used at the 95% level.

Effect of Sex.—In general, males and females showed similar trends in each racial group. Moreover, the average value in each grade and for corresponding age in each sex did not seem to vary significantly apart from weight. It was therefore decided to combine male and female data for all components except that of weight.

I. Grade of Atherosclerosis and Chemical Composition

The question whether chemical analysis provides a satisfactory objective method for determining the degree of atherosclerosis is complicated by two factors. First, since

the grading is subjective, we cannot be completely certain that grading was identical in the two races. Second, the grading is not equidistant; i. e., an aorta classified as Grade 5 is not necessarily five times as severely involved as an aorta classified as Grade 1. This excludes the possibility of curve fitting, as has been undertaken with the analysis in respect to ages (*vide infra*). The most effective analysis obtainable is made by comparing averages between successive grades for each race, and also by comparing the averages for the same grade in the two races.

Dry Weight.—The average weight increases significantly with grade in both sexes and races (Table 1), but the difference between races is not significant for the same grade. Unfortunately, the possible value of dry weight as an objective measurement of grade was not appreciated originally, since it was intended to express our findings as percentage composition, and corrections for height of patient and size of histology blocks were not made. The differences between grades, however, appear too great to be explained by such errors.

Ash.—Ash tends to increase with grade for both races. However, in the same grade, ash values between white and Bantu subjects for Grades 3 and 4 show significant differences (Table 1).

Calcium.—Grading with respect to calcium concentration shows striking differences between Bantu and white subjects. Among Bantu subjects there are some differences between Grades 0 and 1 and Grades 2, 3, and 4, but no clear trend is apparent. Calcium values for white subjects, however, show a very clear trend with increasing grade; Table 2 gives the 95% confidence limits for the average within each grade. The marked overlap of these limits should be noted, indicating that while the grades can establish a calcium trend, there is a tremendous variation of calcium values within each grade. The differences between grades (white subjects only) were all found to be significant except for Grades 1 and 2.

In the higher grades (3 and 4) the mean calcium concentration for the same grade differs significantly between Bantu and white subjects; and the higher the grade the more marked does this divergence become (Table 1).

Total Lipid.—Average total lipid values tend to increase with grade. Differences in values between successive grades for the Bantu are significant except for Grades 1 and 2. With white subjects the values for each grade are significantly different except for Grades 2 and 3. While differences between races for the same grade are not significant, in general, the values for the white subjects are higher than those for the Bantu, except for Grade 1 (Table 1).

Cholesterol.—The trend for cholesterol to increase with grade is clearly shown in Table 1, but there was an immense overlap of observations between the grades. Hence, grading with respect to cholesterol, as with calcium, makes it possible to establish a trend for group data but is unsatisfactory in any particular case. In Table 3, the 95% confidence limits for the average within each grade are given for both white and Bantu subjects, and it will be noted that these limits are wide. The same table shows the results of testing for a difference between the average of successive grades within each racial group. In the case of the white subjects the values were all significant; in the Bantu, only the differences between Grades 0 and 1 were not significant.

The differences in the averages between the races for the same grade were found not to be significant. In all cases, however, the average cholesterol value of the white subjects was higher than that of the Bantu, and the higher the grade the more marked did this difference become.

Phospholipid.—The tendency for phospholipid to increase with grade is unmistakable, but the difference between grades was not significant in either race, nor were the

TABLE 1.—*Changes in the Mean Chemical Composition*

Grade of Atherosclerosis	No. of Subjects				Dry Weight Aorta, Gm.				Ash †		Calcium †	
	Males		Females		Males		Females					
	B	W	B	W	B	W	B	W	B	W	B	W
0	2	0	0	0	5.97	--	--	--	3.03	--	0.70	--
1	13	1	4	1	6.99	5.08	7.33	7.04	3.44	3.60	0.96	1.39
2	10	11	14	5	8.47	8.83	6.98	6.03	4.86	4.24	1.38	1.51
3	14	8	6	5	9.24	9.74	9.22	8.31	5.08	7.59	1.85	2.76
4	3	5	4	13	12.22	13.03	9.61	11.21	5.46	10.75	1.53	4.12
5	0	6	0	4	--	18.36	--	16.01	--	17.65	--	6.81

* B = Bantu subjects; W, white subjects.
† Expressed as grams per 100 gm. dry weight.

differences between the racial groups for the same grade significant.

Total Nitrogen.—A fairly clear decline in nitrogen concentration occurs with increasing grade. The trend is apparent for the Bantu, but differences between successive grades are not significant. With white subjects, only the difference between Grade 4 and Grade 5 was significant, although that between Grade 3 and Grade 4 was fairly marked. When comparing values between Bantu and white subjects for the same grade, white-subject values are consistently lower than values for the Bantu (Table 1).

TABLE 2.—*Range and Mean Values for Calcium in Each Grade in White Aortas*

Grade	$\bar{x}$	$s/\sqrt{n}$	95% Limits of Confidence	Significance Between Grades
1	1.39	0.505	0.38-2.40	N. S.
2	1.51	0.227	1.06-1.97	$P<0.05$
3	2.76	0.384	1.99-3.53	$P<0.05$
4	4.12	0.463	3.19-5.05	$P<0.05$
5	6.81	1.041	4.73-8.89	

Collagen.—There is an obvious decline of average collagen values with grade; grading reveals a similar picture for the two races (Table 1).

Elastin.—No clear trend with grade was discernible. The average elastin value seems to be slightly lower for white than for Bantu subjects except for Grade 4, but the differences do not appear to be very marked.

Hexosamine.—The average values per grade are shown in Table 1, and no clear trend is apparent.

Summary of Changes in Chemical Composition and Pathological Grading

In each grade, the values for any single chemical component show a wide variation not only between races but for the same racial group. On the other hand, the mean values for certain constituents show a definite correlation with degree of atherosclerosis. This correlation is most readily demonstrable for total weight, percentage of total lipid, cholesterol, and phospholipid,

TABLE 3.—*Mean Values of Cholesterol* and Grading in White-Subject and Bantu Aortas*

Grade	White Subject Aortas			Bantu Aortas		
	$\bar{x}$	95% Confidence Limits	Significance Between Grades	$\bar{x}$	95% Confidence Limits	Significance Between Grades
0	/	/ /		1.05	0.83-1.27	N. S.
1	1.50	1.06-1.94	$P<0.05$	1.41	1.14-1.68	$P<0.05$
2	2.41	1.93-2.89	$P<0.05$	2.31	1.94-2.68	$P<0.05$
3	4.40	3.47-5.33	$P<0.05$	3.60	3.01-4.19	$P<0.05$
4	6.15	5.39-6.91	$P<0.05$	4.55	3.87-5.23	
5	8.47	6.74-10.20		/	/ /	

* Expressed as grams per 100 gm. dry weight.

*of the Aorta in Relation to Degree of Atherosclerosis**

Total Lipid		Cholesterol †		Phospholipid †		Total Nitrogen †		Collagen †		Elastin †		Hexosamine †	
B	W	B	W	B	W	B	W	B	W	B	W	B	W
11.3	--	1.05	--	2.19	--	14.3	--	26.1	--	30.8	--	0.86	--
13.7	12.3	1.41	1.50	2.32	1.73	14.8	14.5	23.0	25.3	29.4	26.3	0.80	0.74
14.9	16.6	2.31	2.41	2.84	2.87	14.3	13.7	22.8	22.5	30.2	28.9	0.92	0.83
16.9	18.4	3.60	4.40	3.12	3.56	13.8	13.1	21.2	20.4	30.8	27.3	0.89	0.86
19.4	22.5	4.55	6.15	3.17	3.65	13.6	12.3	21.0	21.8	27.7	28.3	0.87	0.80
--	27.7	--	8.47	--	4.04	--	10.1	--	20.2	--	21.2	--	0.60

in both races, as well as for ash and calcium in white subjects. These findings are in agreement with the experiences of previous workers.[6,7,15-20] Other constituents show less prominent differences, although they might have proved of significance had the number of aortas studied been greater.

There appears to be no great difference for the two races up to and including Grade 3 in respect of dry weight, total lipid, and phospholipid. However, with respect to ash, calcium, and cholesterol, certain obvious differences are apparent after Grade 2 which we believe represent qualitative differences in the atherosclerotic process in the two races. Accordingly, while it may be possible to utilize chemical analysis for grading atherosclerosis for group data within one racial group, it would appear inadvisable to use components such as calcium and cholesterol as accurate indices of atherosclerosis in different races. It should be noted that such a simple measurement as dry weight may prove as satisfactory an estimate of degree of atherosclerosis as the more complicated determinations.

The significance of these qualitative differences in the aorta in relation to the complications of atherosclerosis in the smaller vessels requires investigation, as the correlation between the severity of atherosclerosis in the aorta and coronary arteries is not complete.[21]

II. Age Trends in Atherosclerosis and Chemical Composition

Grade of Atherosclerosis.—The mean grade of atherosclerosis increases with age in both races (Table 4), and severe atherosclerosis tends to be less severe in Bantu than in white subjects in the older age groups. In view of our observations on chemical analysis and grading, this is unlikely to be due entirely to subjective grading error.

Chemical Changes.—While changes in chemical composition with age may be mainly dependent on the increasing severity of atherosclerosis with age, a further factor must be considered. There were sufficient aortas available of Grade 2 severity to permit comparison of chemical analysis below and above 45 years of age in both races.

TABLE 4.—*Mean Average Grade of Atherosclerosis in Each Age Group for Bantu and White Subjects*

	Bantu					White				
Age Range, Yr.	Males		Females		Both Sexes	Males		Females		Both Sexes
25-34	0.7	(9) *	1.7	(5)	1.0	1.8	(5)	2.0	(1)	1.9
35-44	2.0	(7)	2.0	(4)	2.0	2.0	(3)	2.0	(2)	2.0
45-54	2.2	(8)	1.3	(3)	1.9	2.5	(5)	2.3	(5)	2.4
55-64	2.4	(5)	2.8	(8)	2.5	3.4	(9)	3.4	(5)	3.4
65-74	2.3	(6)	2.6	(5)	2.4	3.4	(4)	3.8	(9)	3.7
75+	3.1	(7)	2.8	(3)	3.1	4.3	(4)	4.1	(6)	4.2

* The figures in parentheses represent the number of aortas.

TABLE 5.—*Changes in Composition in Aortas with Atherosclerosis of Grade 2 According to Age*

	Bantu Aortas			White Aortas		
	Under 45 (9)* (*a*)	Over 45(15)* (*b*)	Significance Between (*a*) & (*b*)	Under 45 (7)* (*c*)	Over 45 (8)* (*d*)	Significance Between (*c*) & (*d*)
Dry Weight, gm.						
Males	6.39	9.36	$P<0.01$	6.49	11.65	$P<0.01$
Females	4.88	8.55	$P<0.01$	5.31	7.10	--
Ash †	3.60	5.61	$P<0.05$	2.95	5.83	$P<0.01$
Calcium †	1.01	1.60	N. S.	0.91	2.29	$P<0.01$
Total Lipid †	13.9	15.5	N. S.	14.5	19.3	$P<0.01$
Cholesterol †	1.42	2.84	$P<0.01$	1.83	3.16	$P<0.01$
Phospholipid †	2.54	3.04	N. S.	2.68	3.11	N. S.
Total Nitrogen †	14.6	14.1	N. S.	14.1	13.3	N. S.
Collagen †	24.6	21.7	$P<0.05$	24.3	21.5	N. S.
Elastin †	27.5	31.8	$P<0.05$	29.2	28.4	N. S.
Hexosamine †	0.88	0.95	N. S.	0.79	0.89	N. S.

* The figures in parentheses refer to the number of aortas in each group.
† Expressed as grams per 100 gm. dry weight.

These findings are presented in Table 5 and show that for certain constituents significant chemical changes occur with age within the same grade. This observation would indicate that our figures accordingly represent a summation of both aging and atherosclerotic processes, as shown by Haythorn et al.,[18] thus complicating the use of such measurements for objective grading.

Dry Weight.—In both racial groups there is a steady increase in the weight of the aorta with age, confirming observations of previous workers [16,17] (Table 6 and Fig. 2). The increase is, however, less in Bantu than in white subjects after 45 years, and differences between Bantu men and women are less pronounced than between the white sexes.

Ash.—Table 6 and Figure 3 confirm earlier reports [16] in demonstrating an increase in percentage of ash with age, but whereas in the Bantu the mean ash concentration is only doubled in the 75+-year age group as compared with the 25- to 34-year groups, the corresponding increase is fivefold in white aortas.

Calcium.—The changes in calcium concentration follow those in ash (Table 6, Fig. 3) and are in accord with the findings of previous workers.[15-19] This element provides the most striking differences between the two races. From the age of 30 years onward the Bantu show a slow linear increase (Fig. 3), but the data on the aortas of the white subjects can be represented only by a straight line from the age of 40

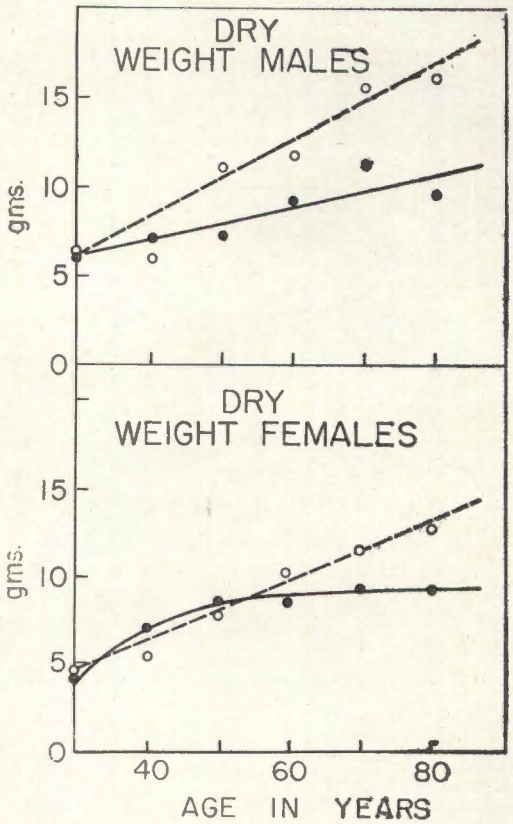

Fig. 2.—Graphs showing changes with age in mean dry weight of aortas for each race. Values for Bantu subjects are expressed by solid line and circles; values for white subjects, by broken line and clear circles.

years onward. The estimated slope of Bantu data after 40 years is 0.021; the corresponding figure for white subjects is 0.122; these differences are statistically significant at the 99% level (u=3.48). In the case of the Bantu, constant variance is assumed, an assumption which is just passable. With white subjects this convenient assumption is no longer possible, but as the standard deviation increased with age, use is made of the hypothesis S. D.=0.055× age-1.550. The equations of the Bantu and white lines are Ca=1.41+0.021 (age-53.7) and Ca=2.33+0.122 (age-50.5), respectively. These racial differences demonstrated above show that the changes in calcium concentration are not alone the result of degree of atherosclerosis or of age.

Total Lipid.—As can be seen from Table 6 and Figure 4, average total lipids in the aorta show a rough linear increase with age, as reported by others. Assuming constant variance for both Bantu and white subjects, slopes were found to be 0.10 and 0.20, respectively. This difference just fails to be significant at the 95% level.

Cholesterol.—In white subjects, cholesterol rises with age in an almost linear fashion (Fig. 4).[6,16,20] With the Bantu, in contrast, cholesterol rises to a maximum between 60 and 70 years and thereafter seems to decrease; the behavior of the data is well represented by curve *b* in Figure 4. If readings taken at the age of 70 and 80 years are ignored, the first four points conceivably form a straight line as given by line *a* in Figure 4. If line *a* is not accepted as being a reasonable representation of the data, we can conclude that the Bantu in the older age groups differ greatly from similar white subjects. Differences between average cholesterol concentrations of Bantu and white subjects "65 to 74" and "75+ years" were tested, and were found to be significant.

Correlation Between Cholesterol and Calcium.—In white subjects, a fairly good linear relationship is apparent between calcium and cholesterol for values less than 7.0 gm. % dry weight. A quadratic curve probably gives a fair representation of the relationship. Correlation values of 0.64 and 0.45 were obtained between calcium and cholesterol for white and Bantu subjects. The Bantu would be expected to be lower because of the curved trend of their cholesterol concentration with age.

Phospholipid.—There is a curved increase in phospholipid with age, as noted by Buck and Rossiter.[20] For both racial groups, a maximum value is reached at about 50 years. At 30 years, values for the two races seem to be identical; thereafter the value for white subjects seems to exceed the Bantu value by a constant amount from about the age of 40 years onward (Table 6 and Fig. 4).

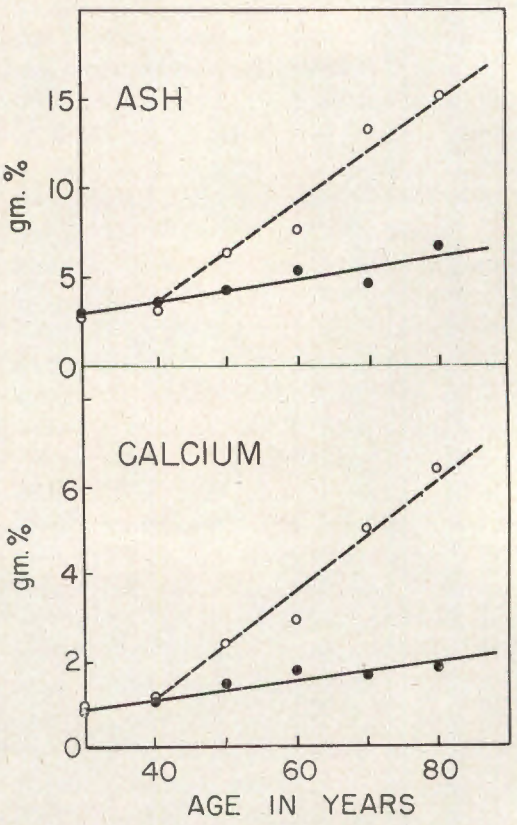

Fig. 3.—Graphs showing changes with age in mean ash and calcium concentrations in aortas for the two sexes combined (grams per 100 gm. dry weight). Values for Bantu subjects are expressed by solid line and circles; values for white subjects, by broken line and clear circles.

TABLE 6.—*Changes in the Mean Chemical*

Age Group	Dry Weight, Gm.				Ash †		Calcium †		Total Lipid †	
	Males		Females							
	B	W	B	W	B	W	B	W	B	W
25-34	6.27	6.52	4.43	4.71	3.00	2.92	0.82	0.86	12.5	13.6
35-44	7.26	6.12	7.25	5.61	3.60	3.20	1.03	1.08	15.1	16.3
45-54	7.46	11.35	8.52	7.95	4.40	6.43	1.48	2.40	15.3	20.6
55-64	9.50	12.12	8.61	10.31	5.39	7.70	1.77	2.97	16.2	20.0
65-74	11.60	16.9	9.44	11.55	4.76	13.53	1.68	5.06	17.6	24.5
75+	9.93	16.46	9.33	12.88	6.83	15.32	1.81	6.21	17.5	23.3

* B=bantu aortas; W, white aortas.
† Expressed as grams per 100 gm. dry weight.

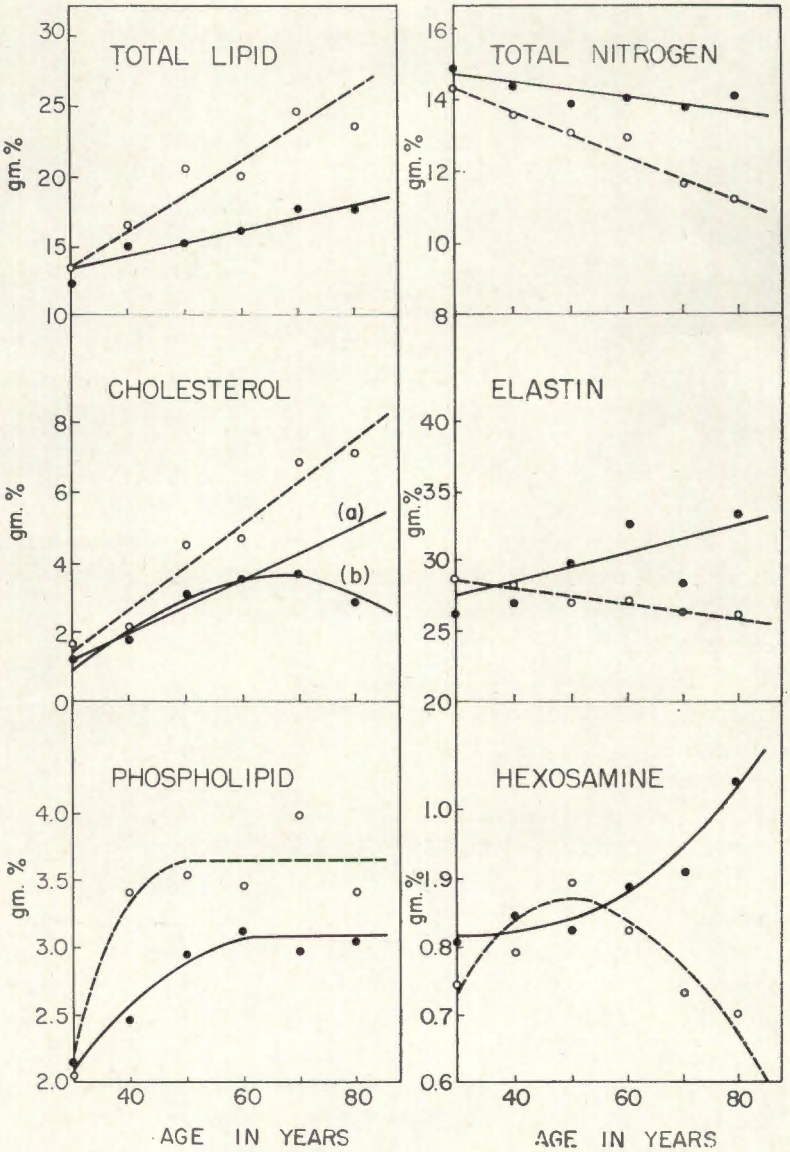

Fig. 4.—Graphs showing changes with age in mean total lipid, cholesterol, phospholipid, total nitrogen, elastin, and hexosamine concentrations for the two sexes combined (grams per 100 gm. dry weight). Values for Bantu subjects are expressed by solid line and circles; values for white subjects, by broken line and clear circles.

Composition of the Aorta in Relation to Age Group*

Cholesterol †		Phospholipid †		Total Nitrogen †		Collagen †		Elastin †		Hexosamine †	
B	W	B	W	B	W	B	W	B	W	B	W
1.22	1.66	2.16	2.05	14.9	14.4	23.9	23.9	26.4	28.8	0.81	0.75
1.78	2.12	2.48	3.41	14.4	13.6	24.1	21.8	27.1	28.3	0.84	0.79
3.08	4.56	2.96	3.54	13.9	13.1	20.9	20.5	29.8	27.0	0.82	0.90
3.54	4.72	3.13	3.46	14.0	12.9	20.2	23.5	32.6	27.2	0.89	0.82
3.68	6.86	2.98	4.01	13.7	11.6	23.0	19.4	28.3	26.3	0.91	0.73
2.83	7.10	3.05	3.42	14.1	11.1	21.6	20.9	33.2	26.0	1.06	0.70

Total Nitrogen.—White subjects show a linear decrease with age (Table 6, Fig. 4). The Bantu data do not give such a satisfactory linear representation, but to make comparison possible a straight line was fitted to the Bantu data as well. The difference in slopes of the lines, 0.019 and 0.066, was found to be significant ($u=3.36$). The assumption of constant variance was reasonable for both racial groups.

Collagen.—There seems to be no racial difference with respect to collagen concentrations, and there is a suggestion that collagen decreases with age, which is contrary to the findings of Faber and Møller-Hou [22] and Myers and Lang.[23] The data, however, are highly variable, and very much larger groups require to be investigated in order to establish a clear trend (Table 6).

Elastin.—The Bantu data are variable (Fig. 4), in contrast to the white-subject data; but the trends are unmistakable, and are well represented by straight lines. These were tested for slope (as being representative of the trend) and found to be statistically significant at the 99% level ($u=4.1$). With white subjects, the variance obviously increases with age. In the latter, a very fair assumption was S. D.$=0.073+0.284$. The white-subject line was found to be elastin$=27.56-0.058$ (age-49.7). The equation of the Bantu line was found to be elastin$=29.80+0.02$ (age-53.7). The white-subject data confirm observations made in the studies of others.[22,23]

Hexosamine.—Figure 4 clearly shows that the data on the two racial groups are radically different with respect to hexosamine. The Bantu show a steady curved increase with age, while the white subjects show a curved increase, reaching a maximum at the age of 50, with a steep decline thereafter. These curves are so different that no further statistical analysis was carried out. These values were determined to give indication of proportion of acid mucopolysaccharide present. Faber used the proportion of sulfate to give indication of chondroitin sulfate, and the above observations for white subjects are in accord with his results.[17]

Histological Examination

It was soon apparent that histological examination was of little value for purposes of grading, thereby confirming the view of Rosenthal.[6] Observations, however, provided some check on the type of lesion present, and the studies confirmed reasonably well the naked-eye appearance of the plaques.

Comment

With increasing age, there are distinct differences both in the severity of atherosclerosis and in the chemical composition of aortas from Bantu and white subjects. Assuming that the aortas constituted comparable samples, our results support the view that severe aortic atherosclerosis in the older age groups is less common in Bantu than in white subjects.

The picture, however, is obscured by the fact that the chemical changes are the result both of atherosclerosis and of age, and further studies are indicated to separate

the effect of each factor. Allowing that part of the differences is due to atherosclerosis, it would still appear that the differences demonstrated are insufficient to explain the markedly different incidence in myocardial infarction and coronary occlusion in the two races if these are a direct function of the severity of atherosclerosis. It is feasible that the correlation between the severity of atherosclerosis in the coronary arteries and that in the aorta varies in different races, but we have no further information on this possibility.

It is usual to correlate the severity of the atherosclerotic process with its complications, notably ulceration and thrombosis; but the present findings indicate that qualitative changes in the atherosclerotic and aging processes may also be considered. For example, the severity of atherosclerosis in two aortas may appear similar not only on gross examination but on cholesterol and weight measurements, whereas the quantity of calcium may be very different. We are unwilling as yet to assess the etiological significance of these qualitative changes within aortas of the same grade, but they may eventually prove of importance in indicating causal factors.

In conclusion, it would seem that while grading by chemical analysis may be of value in one racial group of similar age, its use in regard to different races and different age groups is more doubtful. Furthermore, the simple measurement of dry weight may be as satisfactory as more complicated procedures. Since, however, the use of subjective grading by different authors in different countries and at different times will tend to obscure the relationship of severe atherosclerosis and myocardial infarction, the need of developing objective methods further is clear.[25]

Summary

The dry weight and concentrations of total ash, calcium, total lipid, cholesterol, phospholipid, nitrogen, elastin, collagen, and hexosamine were determined in the aortas from 70 Bantu and 58 white subjects, the aortas being previously graded for the degree of atherosclerosis.

Mean total weight, and lipid, cholesterol, and phospholipid concentrations showed definite correlation with the degree of atherosclerosis in both races. Ash and calcium concentrations showed a correlation in white but not in Bantu aortas. Furthermore, in aortas of the same grade there were differences between the two races in regard to ash, calcium, and cholesterol concentrations. The differences were sufficiently large as to be not wholly explicable on the basis of subjective error in grading, and hence probably represent true qualitative differences in atherosclerosis, especially in regard to calcification. However, there is evidence that considerable changes in chemical composition also occur with age within the same grade, thus obscuring the picture.

Differences in the concentration of various chemical components, notably calcium, cholesterol, and hexosamine, were demonstrated between Bantu and white subjects, especially in the older decades. Further, the mean degree of atherosclerosis and total dry weight were significantly less in Bantu than in white subjects. It is suggested, accordingly, that further racial studies should take into consideration qualitative as well as quantitative differences in the atherosclerotic process. However, these racial differences, if representative of the degree of atherosclerosis and if equally applicable to the coronary artery system, would appear insufficient to explain the marked differences in the incidence of myocardial infarction demonstrated between the two races.

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SOME ASPECTS OF NUTRITIONAL RESEARCH IN SOUTH AFRICA

ALEXANDER R. P. WALKER

Head, Human Biochemistry Research Unit, South African Institute for Medical Research, Johannesburg, and the Council for Scientific and Industrial Research

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SOME ASPECTS OF NUTRITIONAL RESEARCH IN SOUTH AFRICA*

In South Africa, living side by side with the white population, is a large Bantu population which is observable in various stages of sophistication of diet and manner of life. Speaking generally, the diet of these people is probably adequate in calories and total protein, is low in animal protein, fat, and certain mineral salts and vitamins, but is high in carbohydrate and crude fibre. This situation is of interest for at least three reasons. First, because there is evidence that such a diet, directly or indirectly, gives rise to or promotes various departures from "normal," the precise causation and significance of which are still largely obscure. Second, a population consuming such a diet provides a "touchstone" against which may be tested many of the orthodox concepts on (1) recommended allowances of nutrients, and (2) physiologic functions such as lactation and hemopoiesis. Third, the Bantus appear to suffer very little from a number of important diseases in which the nutritional factor is variously implicated. A few examples in these three fields of research will now be given, illustrations being selected mainly from investigations undertaken by the writer and associate workers in Johannesburg.

(1) Departures from "Normal" in the Bantu

Blood. No difference has been found between newborn Bantu and white babies with regard to mean values for fractionated serum proteins, serum cholesterol and esters, and various liver function tests, yet highly significant differences are found between the respective means for the mothers of both races (I. Bersohn, S. Wayburne, H. Hirsch, and C. D. Sussman, *South African J. Clin. Sci.* **5**, *35* (*1954*); Bersohn and Wayburne, *Am. J. Clin. Nutrition* **4**, *117* (*1956*)).

Breast Milk. Bantu mothers consuming a high maize diet, including an apparently adequate intake of niacin (although presumably much of it is in "bound" form) have a breast milk concentration of this vitamin less than half the mean value found in white mothers. This abnormality, not found in Bantu mothers consuming a Europeanized diet, is not believed to be of nutritional consequence (A. R. P. Walker, *Nature* **173**, *405* (*1954*)).

Urine. From balance observations, we have noted that volumes of Bantu urine collected over twenty-four hours are much greater than corresponding volumes from white subjects. This phenomenon, which has often been observed in white subjects on high carbohydrate diets, has not yet been adequately explained (R. A. McCance and E. M. Widdowson, *Med. Res. Council (London) Special Report Series No. 254* (*1946*); D. A. Smith and M. F. A. Woodruff, *Ibid. No. 274* (*1951*)).

Feces. Adult Bantus void daily up to four times the amount of feces compared with white people on a white bread dietary. Using carmine as a marker, the time of passage with the Bantu is found to be shorter, often about one-half that of white subjects. Further, Bantu feces occlude as much as 50 per cent more gas compared with the feces of white persons. Combining these observations, it is clear that *a given volume* of fecal material in the Bantu may pass through the digestive tract many times faster than in white subjects. The effect of this rapid passage on synthesis, breakdown, absorption, resorption, microflora population, morphology of the intestinal tract, etc., has been virtually unstudied. Concerning the digestibility of nutrients, on very high

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cereal diets, R. A. McCance and C. M. Walsham (*Brit. J. Nutrition* **2,** *26* (*1948*)) stated that protein nitrogen is completely digested. Excluding obviously unchewed food (*e.g.*, whole maize and beans) we have not found undigested starch in adult Bantu feces, and not always in the diarrheal feces of infants with kwashiorkor. In regard to fat, large amounts of fat, up to 13 g. per day, are voided when the cereal intake is very high (apparent digestibility of fat 49 per cent); such fecal fat we believe to be mainly of endogenous origin, and *not* composed of unabsorbed fat (A. R. P. Walker, *Nature* **164,** *825* (*1949*); Walker and U. B. Arvidsson, *South African J. Sci.* **47,** *267* (*1951*)).

(2) The Bantu as a "Touchstone" for Orthodox Beliefs in Nutrition

Calcium. The calcium intake of the Bantu is about one third to one half of that usually recommended. The phosphorus intake, much of it in the form of phytate phosphorus, is high. Moreover, where cereals are the almost exclusive source of calories, the calcium: phosphorus ratio is as "unfavorable" as 1:10. The amount of vitamin D ingested is almost nil. There is, of course, plenty of sunlight, although some believe that the dark skin of the Bantu militates against the production of vitamin D from ultraviolet irradiation. To determine the extent to which these people are handicapped by low calcium intake, we have investigated various aspects of calcium metabolism—calcium balance studies, the role of phytic acid phosphorus (A. R. P. Walker, *Lancet* **II,** *244* (*1951*)), serum calcium levels (Walker, U. B. Arvidsson, and W. M. Politzer, *South African Med. J.* **28,** *48* (*1954*)), the composition and histology of bone (Walker and Arvidsson, *Metabolism* **3,** *385* (*1954*); J. Higginson, *Ibid.* **3,** *392* (*1954*)), physical bone density, studies on the incidence of rickets in urban and rural areas, the roles of calcium in influencing growth and in affecting the development of rickets (Walker, *Am. J. Clin. Nutrition* **2,** *265* (*1954*); *Ibid.* **3,** *114* (*1955*); *Nutrition Reviews* **14,** *36* (*1956*)), liability to fractures, and certain comparative radiologic studies. Briefly, in none of these respects can we say precisely where these people are stigmatized by their low intake of calcium. In strong contrast to other nutrients, there appears to be no evidence in man of any syndrome caused *solely* by calcium deficiency or remediable by calcium supplementation *only*. Is it not possible that in different parts of the world, diets which support and maintain life contain enough calcium for satisfactory bone formation and for the other physiologic functions involving the element?

Ascorbic Acid (Vitamin C). Knowing the unsatisfactory composition of the foods used by Bantu mothers in weaning their children, there is no difficulty in forecasting the outcome, which varies from mild malnutrition to the severest forms of kwashiorkor (A. R. P. Walker, D. C. Fletcher, E. S. P. Strydom, and M. Andersson, *Brit. J. Nutrition* **9,** *38* (*1955*)). Predictable stigmata, *e.g.*, retarded growth, edema, dermatosis, etc., are in evidence, yet one deficiency disease, namely, infantile scurvy, is inexplicably absent. We have frequently found that the intake of vitamin C, determined from examination of food prepared by Bantu mothers for their babies, is almost nil, yet clinical and radiologic observations on groups of such subjects have provided no evidence of scurvy. Moreover, plasma concentrations of vitamin C, even in infants with kwashiorkor, have been found to be consistent with an absence of scurvy. Hence, either all Bantu infants have access to sources of vitamin C which neither ourselves nor Bantu social workers are aware of, which we disbelieve, or we are driven to consider that Bantu infants under the conditions of cereal "pap" intake, are able to synthesise vitamin C (Andersson, Walker, and H. C. Falcke, *Ibid.* **10,** *101* (*1956*)).

Lactation. Despite habitual consumption of a diet which, according to current beliefs,

would not be expected to favor normal lactation, Bantu mothers usually produce an abundance of milk and breast-feed frequently for protracted periods. Evidence indicates that their milk has a satisfactory chemical composition; furthermore, since Bantu and European babies when exclusively breast fed are comparable clinically at 6 months, confirmation is provided that Bantu breast milk is adequate in quantity as well as quality. In the face of this evidence it is questionable whether dietary deficiency can be invoked to explain the failure of the large proportion of white mothers to lactate satisfactorily (A. R. P. Walker, U. B. Arvidsson, and W. L. Draper, *Lancet* **I,** *317* (*1952*); *Tr. Roy. Soc. Trop. Med. Hyg.* **48,** *395* (*1954*)). Among the Bantus, the induction of a flow of milk from virgins has been claimed, as well as the capacity to lactate even beyond the menopause (P. J. Greenway, *East African Med. J.* **13,** *346* (*1937*)). At present we are carrying out analysis of "grandmothers' " breast milk. In view of these observations, we have to admit how incomplete is our knowledge of the factors, dietary and non-dietary, which influence lactation.

Hemopoiesis. The factors listed as being important in hemopoiesis are well known. Among the Bantus, their excessive iron intake (as much as 200 mg. per day) results in widespread siderosis, elevated serum iron concentrations, and a low incidence of hypochromic anemia (A. R. P. Walker and U. B. Arvidsson, *Tr. Roy. Soc. Trop. Med. Hyg.* **47,** *536* (*1953*); J. Higginson, T. Gerritsen, and Walker, *Am. J. Path.* **29,** *779* (*1953*)). An interesting question is, what happens to these people, with their high and irreducible iron stores, during episodes of gross malnutrition or undernutrition? Does the anemia to be expected develop or is it hindered? Investigations indicate that satisfactory hemoglobin levels are often maintained, even in grossly malnourished pellagrins (Walker, *South African J. Lab. Clin. Med.* **1,** *36* (*1955*)). Such observations confirm the high priority given by the body for blood production; they also suggest that, *provided the iron reserves be excessively high,* the other dietary hemopoietic factors are of much less importance.

(3) Research in Diseases in Which Diet is Believed to be an Etiologic Factor

Among the Bantu, certainly, there is a high incidence of liver disease, and various deficiency diseases are common. At the same time it must be pointed out that the Bantus rarely suffer from a large number of diseases which exact a high toll of mortality and morbidity among western peoples. Such diseases include appendicitis, gall stones, peptic ulcer, certain types of cancer, and atherosclerosis and coronary artery disease. There is more than suggestive evidence that the pattern of diet consumed by the Bantu is a strong etiologic factor in the prevention of these diseases, and that when these people adopt European food habits, the "protection" is largely lost.

Appendicitis. Among Bantu mineworkers, appendicitis is *one-eightieth* as common as among a somewhat comparable population, namely, American wartime Naval personnel. It may be apposite to quote a well known British surgeon, Zachary Cope, as maintaining that our present knowledge of the etiology of appendicitis is little in advance of what Fitz taught in 1880 (V. Z. Cope, *Brit. Med. J.* **1,** *1242* (*1950*)).

Gall Stones. From a series of about 9000 consecutive necropsies on Bantus and local Europeans, the incidence of cholelithiasis was found to be 2.04 and 13.52 per cent respectively (B. J. P. Becker and C. B. Chatgidakis, *South African J. Clin. Sci.* **3,** *13* (*1952*)).

Atheroma and Coronary Artery Disease. Published studies (A. R. P. Walker and U. B. Arvidsson, *J. Clin. Invest.* **33,** *1358* (*1954*)) have shown that serum cholesterol concentrations are low and rise only slightly with age in the Bantu compared with white subjects; furthermore, the more severe

complications of atherosclerosis in the Bantu are only about one-tenth as common as among comparable groups of Europeans (J. Higginson and W. J. Pepler, *Ibid.* **33,** *1366 (1954)*; *Nutrition Reviews* **13,** *138 (1955)*). The correlation of low fat intake, low serum cholesterol concentration and low incidence of atherosclerosis is indisputable. Nevertheless, we are hesitant over attaching undue importance to the fat intake aspect, and believe it to be premature to go beyond correlating the *total* pattern of Bantu diet with atherosclerosis. In any case, it should be borne in mind that a low fat intake is but one feature of the Bantu diet, and that these people are relatively free from several diseases other than atherosclerosis (Walker, *Lancet* **I,** *565 (1955)*). The general observation that the mean serum cholesterol concentration of elderly Bantus does not rise beyond that of 20 to 30 year old white subjects is paralleled by similar evidence. Thus Bersohn and associate workers have shown that the electrophoretic lipoprotein pattern of elderly Bantus is even "younger" than that of young white subjects. Further, Miss M. Andersson, by determining the chemical composition of a large series of aortas from Bantu and white subjects of different age groups, has shown that, speaking generally, Bantu aortas retain their youth almost perennially, and scarcely exceed in vascular age those of young white subjects.

Conclusion

The few examples given serve to illustrate the wealth of research material available and the wide scope of the fundamental studies that can be undertaken in South Africa. We have no doubt that the answer to many nutritional and disease problems will be afforded by intensive study of the nonwhite populations in this El Dorado of medical research, for in this country we are particularly fortunate in being able to study the Bantu in all stages of transition, from the wandering primitive living off the land in the fastness of the Kalahari Desert, to the fully Europeanized urban dandy, with his zest for Wild West shows, and his partiality to white bread, sugar, and coca cola.

ALEXANDER R. P. WALKER,
Head, Human Biochemistry Research Unit, South African Institute for Medical Research, Johannesburg, and the Council for Scientific and Industrial Research

EDITORIAL: American Journal of Clinical Nutrition.

THE BEARING OF ETHNIC AND REGIONAL FACTORS IN THE INTERPRETATION OF CLINICAL LABORATORY DATA

From time to time, prominent research workers in Africa have emphasized that considerable re-orientation is required of Western clinicians when practicing among Africans.[1,2] It is insufficiently appreciated that a similar re-orientation may be needed in the interpretation of laboratory data on these people. Normally, the bearing of an ethnic, or even a regional environmental factor, seldom enters into reckoning. There is ample evidence, however, that in certain contexts the influence of such factors may be immense, so that interpretations of data on one ethnic or regional group may not be equally applicable to other groups. For illustration, a variety of examples from the writer's own experience, chiefly relating to nutrition, will now be given.

Serum cholesterol level: Many prospective studies in the United States have shown that adults with serum cholesterol levels exceeding 260 mg. per cent are much more prone to develop arteriosclerotic heart disease, compared with the moiety with cholesterol levels well below this figure.[3] In Italy, however, in similar studies, evidence suggests that the upper cholesterol level cited instead of being 260 mg. per cent, may be lower, perhaps as low as 200 mg. per cent.[3] Among our urban South African Bantu, an increasing proportion of the more sophisticated have high serum cholesterol levels (many have values over 240 mg. per cent, and not a few over 300 mg. per cent);

p.3 and page 2. in reversed position.

yet, despite several decades of westernisation, myocardial infarction in these people continues to remain rare.[4,5] Hence, in seeking to assess the risk of future coronary heart disease using serum cholesterol concentration as a basis, it is clear that prognosis depends on the population group concerned.

Serum iron concentration: Elevation of level of serum iron may arise from idiopathic haemochromatosis, transfusional siderosis, or liver dysfunction.[6] But it may also arise, as is the case with the South African Bantu, from habitually high iron intake or iron "overload".[7,8] While a sustained high level in the serum, say, 200 µg. per cent, in a White person may have serious import,[6] a correspondingly high level in an adult Bantu may be of far less significance.

Serum calcium concentration: Serum calcium levels in less privileged populations in Africa and the East are about 10 per cent lower than in Whites.[9] Some have interpreted this phenomenon as indicative of sub-optimal calcium metabolism.[10] Yet in Bantu, the low levels cited are compatible with absence of unequivocal deficiency stigmata. Hence, in populations habituated, inter alia, to a low calcium intake, a low serum calcium level is not necessarily pathognomonic.

Erythrocyte sedimentation rate: Abnormally high E.S.R. values, not yet explicable, are very common among the Bantu and similarly placed populations.[11] Values of 20 - 50 (Wintrobe scale) are frequently encountered in school children, yet are consistent with excellent attendance at schools, aptitude at lessons, and good prowess in the Harvard Step Test. Correspondingly high values in Whites are consistent with usually obvious and often serious ill health, stemming from degeneration, suppuration, necrosis, or other causes.[6] The interpretation of E.S.R.

is therefore influenced by the population group concerned.

Niacin concentration in breast milk: The breast milk of rural Bantu mothers on a high maize diet has only about half of the mean niacin concentration found in White mothers' milk, although the niacin intake in the former ethnic group is much higher than in the latter.[12] Urban Bantu mothers on a more varied diet, although contributing less niacin, have a higher breast milk niacin concentration than their rural counterparts. The phenomenon is explicable on the basis that part of the niacin in maize is bound and in a form less available for utilization. Thus, the lower concentration of niacin in high maize eating Bantu mothers does not betoken an unusually low intake of the nutrient, as would be the case in mothers in a sophisticated Western population.

Fat absorption and excretion: With an exceptionally high intake of whole grain cereals, wheat and oats, by human subjects, McCance et al. reported unusually high excretions of fat, up to 22 g. per diem, with apparent absorptions of 53 - 76 per cent.[13,14] We have shown that the same phenomenon obtains with Bantu on a very high maize diet.[15] In western populations, apparent absorptions and excretions of these magnitudes certainly would be regarded as grossly pathological;[6] yet they are not pathognomonic under the nutritional conditions described.

Salmonellae and shigellae infections in Bantu children: In serial investigations of stool pathogens in certain

groups of rural children, it was found that in the period of a year, three quarters of the children had one or more episodes of one or both of these infections.[16] Yet they are largely asymptomatic, with only slight effect on temperature, digestion, and absenteeism from lessons, in contrast to the usual adverse response of White children to these infections. We found that the affected Bantu children still display vigorous activity at school games when watched unobserved, and still exhibit outstanding performance in the Harvard Step Test.[17,18] We have noted much the same pattern of behaviour in Bantu school children with bilharzia infections (S. haematobium and mansoni)[17,18] Clearly, pathogens of the type referred to evoke different ill-health pictures in different populations.

Comment: It will be apparent from the illustrations given that in a country including heterogeneous populations which differ in race, nutrition and other environmental factors, caution is required in the interpretation of clinical laboratory data.

Alexander R.P. Walker, Ph.D.
South African Institute for Medical Research,
Johannesburg.

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stronger the concentration the smaller the maximum dose. Thus the dosage is 200 ml. of a 0·5% solution, 75 ml. of a 1% solution and 25 ml. of a 2% solution.[2]

We use blocks for many operations in this hospital, with or without adrenaline, and have proved on a number of occasions that it is only when the maximum dosage for the required concentration is exceeded that convulsions occur.

In my opinion, even with adrenaline the maximum dosage, given above, should never be exceeded.

M. B. Barlow
Senior Anaesthetist
Coronation Hospital
P.O. Box 117
Industria, Johannesburg
8 February 1961

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QUESTIONNAIRE ON NUTRITIONAL DISEASES

To the Editor: Last year the National Nutrition Research Institute addressed a questionnaire to each of approximately 6,000 practising doctors in the country. They were requested to list all cases of nutritional disease which they encountered in their practice during a period of 4 weeks in winter (May/June) and again in summer (November/December). The majority of medical men showed a lack of interest and a relatively poor response was received to the questionnaire. Fortunately some acceded to the request and some supplied more than the data requested. This was mainly the case where doctors practised at hospitals, clinics and mission stations.

At present completed questionnaires are still being received by the Institute and the statistical analysis of the figures has not yet commenced. It is, however, hoped that, in spite of the disappointing response by most of the doctors, valuable data will be obtained from those questionnaires which have been received. It is also expected to obtain interesting data in respect of the milk consumption by children of all races.

The NNRI wishes through the medium of your *Journal* to express its gratitude to all those who collaborated for their contributions. A final appeal is made to all those who have completed their questionnaires, but who have not returned them to the Institute, to do so without delay so that a critical study and interpretation of the data can be undertaken. It must again be stressed that where practitioners have not come across any cases of nutritional disease, this fact should also be brought to the notice of the NNRI.

F. W. Quass
Director, National Nutrition Research Institute
P.O. Box 395
Pretoria
10 February 1961

URINARY CALCULI IN THE BANTU

To the Editor: The interesting paper by Dr. Wise and Professor Kark on 'Urinary calculi and serum-calcium levels in Africans, and Indians'[1] serves to confirm and underline the rarity of urinary calculi in the Bantu compared with its relative commonness in Indian and White populations. Its occurrence in Indians in India is patchy, but the cause of the condition and its irregular distribution is far from apparent. In New Delhi, which I recently visited, the condition of urinary calculi is common, especially in young people, yet every avenue of investigation so far has yielded negligible information of value. Investigations have included 'clinical appraisal with special reference to dietary and nutritional status, serum calcium, phosphorus, and alkaline phosphatase, citrate and mucoprotein levels of the blood, serum proteins, sodium and potassium, histological and histochemical study of the matrix of stones, and histological study of the wall of the bladder. A routine study of pH and bacteriology of urine was made'.[2] It is plausible, of course, to regard the occurrence of urinary calculi as one of the manifestations of chronic malnutrition, and many years ago McCarrison,[3] on the basis of his experimental studies, attached chief blame to a deficiency of vitamin A. Subsequent research, however, has provided no unequivocal evidence in support of this theory. The uncertainties in the aetiology of the condition place it in the same category as crypotogenic 'nutritional' heart disease, and possibly gynaecomastia as seen in Africans, both of which were once confidently attributed purely to faulty nutrition, whereas it has to be confessed that now we no longer have that assurance.[4] Our lack of knowledge presents a challenge, but one which is very difficult to meet; moreover, help is unlikely to be forthcoming from animal experimentation.

The suggestion that liver dysfunction, indirectly, may help to protect the Bantu from urinary calculi is interesting. Nevertheless, among many under-privileged populations elsewhere, which are characterized by equal or greater liver dysfunction, urinary calculi are common.

The suggestion that changes in drinking and other habits may have a bearing on the condition has been made in a recent epidemiological investigation of urolithiasis in Israel.[5] In 12 settlements with a total of 30,292 inhabitants there were 357 patients with urolithiasis (11·8 per 1,000), men being affected much more than women. There was a wide range of incidence in the settlements, from 1·6 to 34·1 per 1,000, according to age, country of origin and length of stay in the settlements. Among immigrants from the Middle East and North Africa there were 7·9 cases per 1,000, and in those from Europe, 27 per 1,000. A high incidence was associated with a low fluid intake, largely the result of transfer of drinking habits from European conditions, and low output of urine caused by large extrarenal fluid loss in conditions of heat and heavy manual labour.

I do not agree with the statement that 'the serum-calcium level is independent of the dietary intake' of the element. There is a good deal of evidence that populations habituated to a diet, *inter alia*, low in calcium, have relatively low serum-calcium concentrations, and *vice versa*.[6,7] To what extent these low levels are due to a low intake of the element or to other factors, is not known. As far as I am aware, low values have not been markedly elevated by ingesting calcium salts only. At this centre, however, we are seeking to throw some light on this aspect by determining serum-calcium levels in Bantu consuming similar diets but imbibing water of grossly different calcium concentration.

Alexander R. P. Walker
Human Biochemistry Research Unit
South African Institute for Medical Research
Johannesburg
14 February 1961

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HEART DISEASE IN PREGNANCY

To the Editor: Mr. M. B. E. Sweet[1] has drawn attention to the dangers of sudden collapse and death of the cardiac patient in the third stage of labour and in the first 12 - 18 hours after delivery. Another dangerous period occurs a week after delivery, when the patient appears to be making good progress. Again, the chief cause of death is sudden heart failure; acute pulmonary oedema is not uncommon, and rarer causes are massive thrombosis of the deep pelvic veins, pulmonary embolism, and even mesenteric thrombosis. The last 3 conditions are nearly always associated with Caesarean section in Grade III or IV patients.

The prognosis of cardiac disease in pregnancy, particularly of mitral stenosis, may be very deceptive, since sudden death can take place at any stage of pregnancy. Many practitioners have experienced at least one or two such cases. A typical example is that of a young primigravida with a Grade I mitral stenosis. An experienced cardiologist had given very good prognosis when she was 2 months pregnant, yet 2 months later she died suddenly from acute pulmonary oedema.

Everyone agrees that cardiac patients should be under

Council on Foods and Nutrition

Symposium on Human Calcium Requirements

The minimum requirements for dietary calcium for humans have not been established. It is generally agreed that there is no convincing evidence of harm at intakes of slightly less than 300 mg/day or as high as 2,000 mg/day in normal individuals. There is disagreement, however, about minimum dietary requirements for calcium for all age groups. Some believe that the Recommended Dietary Allowances of the National Research Council are too high; others believe they should be increased for certain individuals.

The Council on Foods and Nutrition has authorized the publication of the following papers, which present the views of six authorities in the field.

PHILIP L. WHITE, ScD, *Secretary*

I.—*D. Mark Hegsted, PhD, Boston:* There are no data available which allow a satisfactory estimate of calcium requirements. It is now established beyond doubt that the estimation of the amount of calcium required to maintain calcium balance in adults, the information upon which the adult Recommended Daily Allowance for calcium [1] is based, is not a valid estimate of calcium need. This finding is demonstrated by the ability of both animals and man to maintain calcium balance over a wide range of calcium intakes and the fact that the amount required to maintain balance is largely determined by the past dietary history.[2, 3]

Although much of the world's population consumes diets very low in calcium as compared to our current standards, there is no evidence of any clinical condition which can be classified as calcium deficiency. We do not know whether intakes of 1 gm/day are better or worse than half that amount or even less.

We must remember that adaptation to the diet we consume is a necessary condition for life. Adaptation to high, low, or intermediate levels of calcium intake is achieved by adjustments in absorption and excretion so that neither too much nor too little calcium is retained. The mechanism is unknown. Although we commonly measure adaptation to calcium intake by balance experiments, it is obvious that this technique is not satisfactory to determine whether or not adaptation is complete; that is, whether optimal health is achieved at any particular level of intake. New techniques are needed, but so far few ideas have been advanced.

Theoretically we should be better equipped to estimate calcium requirements of children than of adults since children have to retain sufficient calcium to build a skeleton. Estimates have been made of the rates of calcium deposition which may occur,[4] but the necessity or desirability of such rates at different ages is not supported by data. Furthermore, the balance data often reveal such high levels of calcium retentions that they cannot be interpreted in terms of requirements. It is known that errors inherent in balance studies tend to give excessively high figures for calcium retention. The differences in efficiency of absorption which are reported probably reflect differences in customary calcium intakes. Depending on the assumptions made as to the efficiency of absorption at different levels of intake, estimates of requirements can be reached which differ by at least 100%. On the basis of theoretical estimates and of the limited evidence available in areas where calcium intakes are not high, there is reason to believe that normal skeletons are formed with intakes much below those currently recommended.

The calcium needs are probably large during lactation. Yet, the multiple stress of repeated pregnancy and lactation superimposed on a low calcium intake does not cause osteomalacia apparently nor does it limit the production of normal milk provided the vitamin D needs are met. Whereas theoretical considerations will dictate higher requirements during lactation and pregnancy, even here the evidence is not particularly convincing.

With regard to osteoporosis, the controversy has been presented and discussed by Reifenstein, Urist, Nordin, and Whedon.[5] In Urist's series of studies, low calcium intakes were not more common in patients with osteoporosis than in those without the condition. Certainly osteoporosis is not uncommon in the United States and other countries where the calcium intake is relatively high. Although the data from countries where intakes are lower are insufficient, there is an impression that this disease is not as common as might be expected if low calcium intake were a causative factor. Comprehensive epi-

Recommended Calcium Allowances

	Age	Mg/Day[1]	Mg/Day[11]
Children	0-12 mo	600- 800*	500- 600†
	1-9 yr	1,000	400- 500
	10-15 yr	1,200-1,400*	600- 700
Males	16-19 yr	1,400	500- 600
	Adults	800	400- 500
Females	16-19 yr	1,300	500- 600
	Adults	800	400- 500
	Pregnant	1,500	1,000-1,200
	Lactating	2,000	1,000-1,200

* The Recommended Dietary Allowances of the National Research Council are not expressed in ranges; figures represent allowances through the age brackets.
† Not breast fed.

From the Department of Nutrition, Harvard School of Public Health.

demiological studies should be made immediately. The fact that high intakes of calcium are apparently required to force a positive balance in osteoporotic patients would tend to support the argument that the calcium loss is caused by the disease rather than the reverse. The findings that animals adapted to low intakes retain their ability to conserve calcium into old age may be relevant to the development of osteoporosis.

We are called on, therefore, to propose dietary calcium standards without satisfactory evidence, indeed with essentially no evidence, on which to base them. It becomes, then, largely a matter of philosophy. I have argued elsewhere [6] that there is more evidence of harmful effects of high calcium intakes—hypercalcemias, milk-alkali syndrome, kidney stones, idiopathic hypercalciuria—than of calcium deficiency. As far as I am aware, there is little evidence that high calcium intakes are causative of any of these conditions but high intakes may be detrimental in susceptible individuals. Hence, I object strenuously to dietary standards which force the conclusion that 30% of the US population is not getting enough calcium. We have refused to establish standards for many essential nutrients—potassium, magnesium, pyridoxine, folic acid, and vitamin B_{12}, for example—either because there is insufficient evidence as to the requirement or because the deficiency disease is rare. Nevertheless, the deficiency syndromes associated with many of these substances are reasonably well characterized and they do occur in the US and elsewhere. On the basis of the information currently available, many of these nutrients deserve more attention than calcium.

I believe there are insufficient grounds for lowering the calcium intake of the US population deliberately, although the possible detrimental effects deserve some study. In any event, dietary standards have never been effective in limiting intake. A moderate lowering of our standards is needed to remove much of the unjustified emphasis given to calcium currently. Meanwhile, research should be encouraged to provide some valid answers in this area.

II.—*Harold E. Harrison, MD, Baltimore:* The concept that intestinal absorption of calcium is inefficient and high intakes of calcium are required to insure sufficient calcium retention for growth in the child and to maintain calcium balances in the adult is based on the following observations. Only part of ingested calcium is absorbed. Endogenous calcium contained in the intestinal secretions enters the small intestine and increases the load of calcium requiring absorption.

Vitamin D is required for efficient intestinal absorption of calcium; the fecal loss of calcium is increased in vitamin D deficiency states. Increased concentrations in the intestinal lumen of phytate, oxalate, or unabsorbed fatty acids which form nonionized or poorly soluble calcium complexes also increase fecal losses of calcium. Hypermotility, resulting in the rapid sweeping of the contents of the small intestine into the colon, reduces the absorption of calcium. In the normal individual, with adequate vitamin D intake, the net absorption of calcium does not increase proportionately as intake is increased. For example, recalculation of data from studies of calcium balance by Bogdonoff et al,[7] gives the following information: At calcium intakes averaging 109 mg/day the fecal calcium was equal to or somewhat in excess of the intake. When the intake was raised to 859 mg/day, 210 mg or 28% of the calcium increment of 750 mg was absorbed. When the intake was raised to 1,543 mg/day only 71 mg or about 10% of this second increment of 684 mg was absorbed. These calculations are based on the assumption that endogenous calcium added to the gut in intestinal secretions was the same at all levels.

The effect of adaptation and adjustment to levels of calcium intake and the physiological state of the subject must also be taken into account. If an individual is adjusted to a high calcium intake, change to a low calcium intake at first leads to a negative calcium balance because the intestine continues to reject a large percentage of the calcium ingested. With prolonged low calcium intake the efficiency of absorption increases and fecal calcium loss is reduced. A higher proportion of ingested calcium is also absorbed by the young, growing individual than by the adult. Pregnancy likewise results in increased intestinal uptake of dietary calcium. Presumably, the adaptive response and the effect of growth on calcium absorption represent alterations of intestinal transport of calcium in response to the state of mineralization of the skeleton; the mechanism through which this response is mediated is unknown. Because of these adaptive responses, the estimation of calcium requirement cannot be made by simply determining calcium balance at various levels of intake over relatively short periods. The previous intake of calcium will alter the results unless the balance periods are so prolonged that complete adaptation can be assumed. Such a study has been done with adults by Malm,[3] but it is impractical to examine many subjects over a wide range of levels of calcium intake in this way.

The interpretation of calcium retentions in the growing child at high levels of calcium intake is also difficult. For example, a breast-fed infant receives 0.5 mg of calcium per calorie or about 60 mg/kilogram at a caloric intake of 120 calories/kilogram. About two thirds of this calcium may be retained. The infant fed a standard type of cow's-milk formula with added carbohydrate ingests 1.33 mg of calcium per calorie or 160 mg/kilogram. The calcium retained—as measured by balance

From Johns Hopkins University School of Medicine..

studies—on this diet may be 60 to 80 mg/kilogram which is actually greater than the total intake on a human-milk diet. The breast-fed infant has no obvious deficiency of calcium and it is certainly questionable whether the greater retention of calcium by the infant fed cow's milk can be interpreted as evidence that the infant's need for calcium exceeds that supplied by human milk. There may be a systematic error in balance data when the intake of the substance measured is extremely high in relation to the net retention. If the diet is not completely eaten and the amount lost is underestimated, or if some of the feces or urine are lost, the calculated retentions will be incorrect. It is likely, however, that the skeleton of the growing child can take up more calcium if the calcium intake is increased up to some maximum. It does not follow, however, that the highest calcium retentions are mandatory for good nutrition.

Between the first and tenth year of life the daily retention of calcium needed for skeletal growth has been estimated by Leitch and Aitken [4] to be between 75 and 150 mg/day. This level of calcium retention can be maintained on a daily intake of 600 to 800 mg of calcium (approximately 0.4 mg of calcium per calorie); ranging from 60 mg/kilogram at 1 yr to about 25 mg/kilogram at 10 yr. During the period of prepubertal and pubertal growth spurt, retentions of calcium increasing up to as much as 400 mg/day have been estimated as necessary to maintain the state of mineralization of the rapidly growing skeleton. Such retentions are possible with calcium intakes of 1,000 to 1,500 mg or about 0.3 to 0.4 mg of calcium per calorie and about 25 mg/kilogram. After cessation of growth, a calcium intake of 600 to 800 mg or about 0.25 mg of calcium per calorie and 10 mg/kilogram can maintain calcium equilibrium in the vast majority of subjects, other than the pregnant and lactating woman.

The figures cited are not minimum values and adaptation to lower levels of calcium intake is certainly possible. Whether low intakes of 300 to 400 mg of calcium per day for children or adults should be recommended if larger amounts of calcium are readily available is certainly debatable. In populations adapted to these low levels of intake, skeletal mineralization can apparently be maintained. However, it must be remembered that the stature and skeletal mass of the short Peruvian Indian, whose calcium intake is estimated to be below 250 mg/day,[2] is much less than that of the average adult in this country. Extrapolation of data from one group to the other would be hazardous.

The calcium allowances suggested by the Food and Nutrition Board of the National Research Council are almost certainly above minimal needs. In view of the ability of most individuals to adapt to varying levels of calcium intake, dietary calcium intakes both below and above these allowances are compatible with good nutrition. There seems to be no need to recommend extremely high levels of calcium intake except in special cases. Those patients with osteoporosis in whom careful studies have indicated that calcium intakes much above ordinary allowances are needed to achieve calcium retention are exceptions.[8] The possibility must be considered that high calcium intakes from childhood on may alter the physiology of calcium absorption, that intestinal absorption of calcium may be reduced to a minimum with urinary calcium excretion fixed at a relatively high level, and that negative calcium balances could result in late adult life despite ordinarily adequate calcium intakes. There is no evidence, however, to support or refute this hypothesis at the present time. There are, apparently, individuals who have relatively high urinary outputs of calcium which do not diminish when dietary calcium intake is reduced and who therefore go into negative calcium balance. This difference in urinary output may represent individual differences in renal tubular function rather than effects of diet or other environmental factors.

III.—*Ragnar Nicolaysen, MD, Oslo, Norway:* Deficiency diseases play an important role in the evaluation of nutritional requirements.

The establishment of balance or of saturation has little physiological meaning in itself. There must be a correlation with physiological functions or frank disease.[9]

The existence of a calcium deficiency disease has never been clearly established. Hegsted has phrased it with acuity: "Calcium is a nutrient in search of a disease." For this reason many feel that human dietaries, as consumed in various parts of the world, contain sufficient calcium to cover the needs of the majority of the populations.

Recently, interest in old-age osteoporosis has been revived.[5, 8, 10] There is some evidence in favor of the view that old-age osteoporosis is a calcium deficiency disease. Nordin [5] reported relief of symptoms of osteoporosis in a number of elderly persons. He claims that such persons retain calcium avidly over long periods. Some of the reported retention figures are much too high to be representative of true long-term retention and the clinical evaluation of cures is at times beset with difficulties. But it must be hoped that this revived interest will result in definitive work. Meanwhile I still believe that my evaluation [9] in 1960 is justified:

> The possibility still remains that the demineralization process in persons with osteoporotic tendencies can be slowed down with the aid of a diet rich in calcium and what perhaps may be just as important, additional vitamin D.

At a recent meeting of the FAO/WHO Expert Group on Calcium Requirements we discussed the problem of minimum calcium requirements for

From The Institute for Nutrition Research, University of Oslo.

adults and elderly persons. The Group agreed that they could not define a precise minimum figure. The term "suggested practical allowance" [11] was adopted, and defined as "the intake at which the needs of the great majority of persons in any defined population group are likely to be adequately met" (400 to 500 mg/day for adults). Such an approach to a practical recommendation appears to me to be well substantiated by world-wide experience. Of course there is a possibility that some individuals (perhaps 1 in 1,000) may suffer long-term negative calcium balance with an intake of 400 to 500 mg of calcium daily over several decades, with the consequent development of osteoporosis. The most important argument against this possibility is presented by reports that osteoporosis is not common in geographical areas where the intake of calcium is habitually low. However, it may be argued that in the Eastern World people die earlier, and that many persons are not under such good medical supervision as is common in countries with highly developed medical services. It can also be argued that many may tolerate moderate osteoporosis without calling a doctor.

This is all speculation, but it is not unwarranted to draw attention to the situation existing 60 to 70 yr ago in the now highly developed countries. Many people suffered from backache, lumbago, and sciatica then. The tools for precise diagnosis were not available, and time and patience cured many diseases now treated by only partly successful modern therapy. I venture to suggest that close and intense medical scrutiny of persons in areas where calcium intake is low may still reveal that pathological conditions such as osteoporosis are more common than is now recognized.

Some support for the view that osteoporosis can be prevented with the aid of a more liberal intake of calcium than the "suggested practical allowance" can be found in various observations of calcium balance in osteoporotic and elderly persons. Most recently Whedon [8] has produced some evidence in favor of such a view. From this institute, Malm [3] conducted long-term studies with 39 adult males. Three elderly men retained calcium avidly over several months. Even more important are the data for one man, 50 yr old, who remained in balance for more than 300 days while ingesting about 900 mg of calcium daily. However, his balance was negative during the successive 450 days on a daily intake of 550 to 750 mg of calcium. His urinary calcium was high (300 to 350 mg daily) and not at all adapted to the continuous calcium drain. Data for two other subjects in this study suggests that such a response may not be too uncommon.

Perhaps it is warranted to state that there is no easy solution to a complex problem. I subscribe fully to the "suggested practical allowance" because a standard which can be applied with reason in regions of low supply of calcium was and is needed.

IV.—*G. Donald Whedon, MD, and Leo Lutwak, MD, Bethesda, Md.:* The recent demonstration that the strength of bone is related to the degree of its mineralization [12] intensifies current interest in the possible influence of the level of calcium in the diet on the mineralization of bone. Careful studies of this latter relationship are essential for a correct statement of human calcium requirements adequate for development and maintenance of the skeleton.

Investigation of dietary calcium requirements, as well as of other factors which may promote mineral storage, is of even greater interest to those concerned with adult health and gerontology because of growing recognition of the high incidence of the demineralizing disorders, postmenopausal and senile osteoporosis. Urist,[5] Gershon-Cohen,[13] and Smith [4] have demonstrated that osteoporosis, sufficiently severe to produce vertebral compression, was present in 26% to 29% of more than 300 ambulatory women over 50 yr of age who were studied.

The quantity of calcium in the diet has been of little concern to nutritionists because of the observation (in certain population groups of younger age) that adaptation to low intakes may occur through decreased excretion. Malm [3] has shown, however, that some persons cannot adapt to low intakes, but remain in negative calcium balance for long periods. In osteoporosis, the significance of calcium intake has been generally disregarded because the classic concept of the disease is that it is an affection primarily of the protein matrix of bone, demineralization occurring secondarily as the result of too little bone formation. Recently, this concept has been challenged and attention is being focused on impairment of availability and of retention of calcium as a prime factor in this disease.

The probable importance of calcium in osteoporosis has been indicated by various bits of evidence, individually inconclusive but collectively impressive. These have been summarized by Whedon [8] and reviewed in detail by Nordin.[15] Evidence includes the demonstration that calcium deficiency without lack of vitamin D produces osteoporosis, rather than rickets, in several species of animals; the somewhat more frequent occurrence of hypercalciuria among osteoporotic patients than among control patients; and the indication from dietary surveys that habitual mineral intakes are significantly lower among osteoporotic patients than among nonosteoporotic individuals of the same age. In addition, radioisotopic studies of calcium dynamics in various bone diseases—with allowance for the considerable assumptions required by the method—have shown expected abnormal rates of incorporation of calcium into bone. In osteoporosis, however, rates were found at least equal

From the Metabolic Diseases Branch, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health.

to normal,[16, 17] when lower than normal rates would be expected in order to coincide with older ideas of diminished bone formation. A considerable number of short-term, and a few, more valid, long-term metabolic balance studies have indicated that in a probable majority of osteoporotic patients calcium balance can be achieved with a high calcium intake.[8, 10, 15] A significant aspect of these studies has been the considerable individual variation in the amount of calcium required to achieve a positive balance.

These new findings have suggested an alteration in the concept of osteoporosis, namely, that attention be directed once more toward nutritional factors in its etiology.[8, 15] Since calcium levels must be kept within physiological limits for coagulation and neuromuscular functions and there are certain obligatory losses of calcium in urine, stool, and sweat, calcium in an amount equivalent to output must be supplied from the diet. If dietary sources are insufficient, if intestinal absorption is inadequate, or if losses cannot be reduced in those who cannot fully adapt, calcium is drawn from the body storehouse, bone, probably initially from trabecular areas and later from cortical areas. Gradual bone resorption, at a rate greater than that of formation, may thus be the principal mechanism through which osteoporosis develops, probably over several decades. This concept is supported by recent microradiographic observations of the human skeleton by Jowsey [18] which indicate that resorbing surface increases with advancing age without any change, either decrease or increase, in bone-forming surface. This concept does not confine investigation of or enthusiasm for numerous factors, hormonal and other, which may affect calcium balance, but focuses attention on the central essential nutrient for mineralization of bone, calcium.

If calcium insufficiency is a significant etiologic factor in the now frequent osteoporosis of old age —which has its probable origin during middle age— serious thought must be taken before a suggestion is made regarding a reduction in adult requirements. On the one hand, adaptation of certain individuals to low calcium intakes and, on the other, both the higher mean intake level and spread in the level needed to place and keep osteoporotic patients in positive calcium balance suggest much variation in calcium requirement among different individuals. While part of any population might subsist in health on a calcium intake of less than 800 mg/day, a substantial proportion may require much more. A recent review [8] of the effects of high calcium intakes (in the absence of excessive amounts of alkali or vitamin D) did not reveal evidence of harm.

The discovery of simple procedures which would identify those individuals who require high levels of calcium intake would be very useful; presently this information can only be obtained by metabolic balance studies extending over many weeks. Much more data are needed for all age groups to determine the range of daily calcium intakes required to maintain the integrity of the skeleton.

V.—*Alexander R. P. Walker, PhD, Johannesburg, Union of South Africa:* In seeking to determine the calcium requirement for humans it is necessary to know the amount below which specific deleterious effects occur. When a diet is abnormally low in calories, or in nutrients such as iron, iodine, or vitamins C and D, the stigmata which result are predictable, and in general remediable with supplements of the relevant food component. With calcium, however, the situation is different, because the signs of deficiency are not known with certainty. The main obstacle to enlightenment is that diets low in calcium usually are low in other essential nutrients. Perhaps the most rewarding approach to the subject would be the study, at various levels of habitual intake, of the integrity of physiological processes in which calcium, directly or indirectly, is involved. The most appropriate groups for study are (1) the lower socioeconomic stratum of population groups, particularly those persons dwelling in underdeveloped countries, and (2) the segment of such populations most avid for calcium, ie, growing children and pregnant and lactating women.

Turning first to growth, children under favorable nutritional and other environmental conditions undoubtedly grow more rapidly than those less favored. The same applies, although in lesser measure, to ultimate height at maturity. Nevertheless, there is no unequivocal evidence that a low calcium intake is an actual deterrent to rate of growth.[19] Limited studies on South African Bantu groups consuming the same type of diet but imbibing waters of grossly different calcium concentration and studies on Central American groups consuming tortillas treated or not treated with lime do not support the view that the level of calcium intake is a critical factor in determining rate of growth. In any event, it is questionable whether inferior height of children or adults otherwise healthy is essentially a disadvantage.

Because bone contains more than 99% of the total body calcium, it would seem logical under conditions of low calcium intake to look for abnormalities of bone; whether in percentage composition, mineral matter per unit volume, percentage total bone per body, or bone structure. Except in cases of severe rickets, bone from persons whose calcium intake is low does not seem to be abnormal in regard to percentage composition, structure, and liability to fracture.[20, 21] Absence of rickets, also of osteomalacia, is compatible with a habitually low calcium intake; moreover, sound teeth are found more often in backward populations

From the South African Institute for Medical Research.

whose diet is low in calcium,[22] *inter alia*. Paucity of evidence does not allow conclusions about percentage total bone per body in populations accustomed to different intakes of calcium. Much the same lack of knowledge prevails regarding mineral matter per unit volume of bone, which measurement reflects incidence and severity of osteoporosis. However, limited knowledge of this particular for underprivileged populations[23] does not suggest lower physical bone density. Recent evidence indicates that lower retentions of calcium and a higher incidence of osteoporosis correlate generally, but not invariably, with lower calcium intake.[15] If this correlation were found to obtain universally, then wide differences in the incidence of osteoporosis would be expected to prevail between different socioeconomic classes. Moreover, in the lower classes, especially in backward countries, the highest incidence of osteoporosis should be among older women with repeated pregnancies and long lactations. Nevertheless, Seftel[24] has observed that osteoporosis in the Bantu is more common in men than in women.

There is little doubt that, among populations whose calcium intake customarily is low, the mean serum calcium level is lower than in more favored populations.[25] The lower level of serum calcium is regarded by some authorities as pathological. I do not think the lower level of serum calcium is more pathological (in the absence of clinical or other stigmata) than the lower levels of serum cholesterol or of blood sugar in such populations, or their higher mean levels of total serum protein or magnesium.

It is known that calcium has a metabolic role in blood coagulation, also in urolithiasis, cholelithiasis, and tetany. But knowledge is lacking on the precise bearing of levels of calcium intake on these conditions.

The present state of knowledge is inadequate to define human calcium requirements. Certainly, when data on body mineral composition of young healthy subjects from widely different populations are available, it will be possible to calculate minimum daily retentions of calcium necessary to permit satisfactory skeletal formation. But until such information is forthcoming, and until knowledge of osteoporosis is more advanced with respect to the significance of sex, age, race, socioeconomic status, activity, and calcium intake, it would seem advisable not to recommend specific changes in national dietaries.

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PART II CONTINUED : STUDIES BEARING ON THE METABOLISM OF IRON BY THE SOUTH AFRICAN BANTU.

STUDIES BEARING ON THE METABOLISM OF IRON BY THE SOUTH AFRICAN BANTU.

1. IRON INTAKE AND EXCRETION IN THE BANTU.

(i) The high intake of iron.

In underprivileged populations it is usual for the iron intake to be relatively low, since foods rich in iron, e.g. meat and eggs, are expensive. This is particularly the case with indigenous populations dwelling in the tropics and semi-tropics. The ill effects of the usually low iron intake, moreover, are aggravated by the added burden of infections, especially those involving blood destruction or loss (malaria, ancylostomiasis, bilharzia). Accordingly, it is normal for there to be a greater prevalence of iron deficiency anaemia in such people compared with White populations. The adverse situation is manifested especially in the vulnerable groups, namely, children, pregnant women, and old people.

Among the South African Bantu, the scarcity of published information on the prevalence of iron deficiency anaemia should have prompted enquiry into possible sources of adventitious iron in their diet. The source of this iron was discovered fortuitously in 1948 by the writer when carrying out mineral salt balance studies on Bantu prisoners in the Johannesburg gaol.[32] In these investigations it was found that iron intakes and faecal excretions ranged from 40 - 100 mg. per diem. Research revealed that the adventitious iron was derived almost wholly from food preparation vessels. Subsequently, many laboratory studies were carried out in which numerous types of Bantu foods were cooked in the familiar iron "kaffir pot", also in the less frequently used paraffin can. The foods cooked included maize and maize products, "kaffir corn" (sorghum vulgare), legumes (beans, "cow peas"), and vegetables (sweet potato, pumpkin, "kaffir" spinaches). This laboratory work was paralleled by

determinations of iron concentration in various Bantu foods, as prepared by themselves, especially the acid fermented cereal foods, "sour porridge" (magou) and "kaffir beer", which have a pH value of 3.5-5.0, and are consumed in variable although often large volumes by adults.

Regarding ranges of intake, - in the case of children, their intake from everyday foods may be increased by 50 - 100 per cent from adventitious sources, i.e. from about 12 mg. to 20 - 25 mg. per diem. The intake of Bantu men may often exceed 50 mg. per diem, and occasionally 100 mg. or more per diem, particularly at weekends or on festive occasions. Most Bantu women would seem to be exposed to an intake of iron lower than that ingested by men.[32,42,43,44]

(ii) Iron concentration in stools.

A check on these high intakes has been afforded by determining the concentration of iron in stools, a procedure especially easy in rural districts since almost all Bantu, especially children, when living on their traditional high residue diet, can pass stools on request. Previous studies have shown that rural Bantu adults on an average void 50 - 70 g. dry faeces per diem. Hence, reckoning iron concentration on stools of this magnitude, large excretions of the element were found, in one case exceeding 300 mg. per stool. These studies, while lacking in accuracy, have provided abundant confirmation of the unusually high intakes and faecal excretions of iron occurring so frequently among these people.

(iii) Iron concentration in urine.

The amount of iron excreted per diem in the urine of Bantu was not found to be increased, but to lie within normal limits, i.e. 0.1 to ~~0.5~~ 1.5 mg. Fe per diem.[44]

(iv) Comment.

A high intake of adventitious iron by man is not a rare phenomenon. Experimentally, in 1945, McCance and Widdowson demonstrated that occasionally large amounts of iron may be taken up during the cooking of certain every-day British foodstuffs. In India, in 1938, Ranganathan showed that "the accretion of iron which may result from iron contamination during food storage and preparation, may be very considerable". Recently (1963), attention has been drawn, by MacDonald and co-workers (Boston, U.S.A.), to the high concentration of iron occasionally found in wine. However, it is seldom for such adventitiously enriched foods or drinks to be consumed excessively by Whites, thereby contrasting strongly with the often large amounts of cereal products habitually prepared and consumed by the Bantu.

2. ABNORMAL IRON DEPOSITION OR SIDEROSIS IN THE BANTU.

(i) Earlier hypotheses.

As far back as 1929, Strachan, in Johannesburg, noted how frequently the livers of adult Bantu at necropsy were bronze in appearance, and gave an intense blue stain with acid ferrocyanide solution. Strachan considered that this widespread abnormal iron deposition or siderosis was due to ~~the~~ noxious metallic poisons, - copper, tin, and zinc. In 1945, Gillman and Gillman renewed interest in the aetiology of the condition by ascribing it primarily to malnutrition and pellagra. In 1948, and thereafter, the writer, arising from the balance observations described on Bantu prisoners, suggested that the primary cause of the condition was the usually high iron intake (iron "overload").[43,44]

(ii) The iron "overload" hypothesis.

This hypothesis rests on three cardinal points:-

1. The iron intake of Bantu, particularly that of adults, is unusually high, not necessarily habitually so, but certainly intermittently.

2. There is a sufficiency of evidence that a high intake of iron invariably is accompanied by excessive absorption, whether the consumer be in need of iron or not.

3. Iron once absorbed is retained, unless lost by haemorrhage. Excretion of the element into the bowel is very small.

Briefly, the writer has postulated that consumption of a high iron intake, whether regularly or intermittently, in the absence of significant blood loss, ultimately causes siderosis. The cardinal points (2) and (3), primarily, are based on the pioneer work of McCance and co-workers on iron absorption and excretion. The hypothesis, of course, does not exclude the operation of other influencing factors.[42-47]

3. THE SEQUELAE OF SIDEROSIS.

(i) Serum iron levels and iron binding capacity.[48-51]

The level of iron in the serum is influenced by a number of diseases and conditions. There are elevations in idiopathic haemochromatosis, transfusional siderosis, dietary siderosis, and certain infections. Levels are reduced in iron deficiency anaemia and in pernicious anaemia during remission.

Studies on groups of Bantu males have revealed the mean "normal" value of serum iron to be approximately double that for White males; the "normal" value for females is about 30 per cent higher than that of White females. Studies on total iron binding capacity have shown Bantu males to be, on an average, 70 per cent saturated, and females, 40 per cent saturated. These situations contrast with that in idiopathic haemochromatosis where iron binding capacity reaches 90 - 100 per cent saturation.

Our studies indicate, broadly, that elevation of serum iron correlates with extent of iron stores; the relationship, however, is by no means invariable.[50]

(ii) Haemoglobin and haematocrit levels.[52-56]

School children: As indicated in Part I, extensive studies, involving observations on several thousands of Transvaal Bantu children, have revealed that iron deficiency anaemia is very uncommon.[11]

Adult males: Several studies on Bantu males indicate high levels for haemoglobin and haematocrit. In regions where parasitism is no problem, mean levels of these components would appear to be as high as in White males, and in certain groups, even higher.

Adult females: A number of studies ~~of~~ on Bantu females (including pregnant women) have revealed a far lower frequency of iron deficiency anaemia than that prevailing in possibly all otherwise comparable groups of underprivileged women in the tropics and semi-tropics. In respect of iron deficiency anaemia in pregnant women, certain Bantu groups are more favourably placed than the poorer moiety of White women. Other local workers have noted the high mean haemoglobin values in Bantu women.

There is no doubt that the favourable situation in Bantu school children, and men and women, is due to their high iron intake.

(iii) Anatomical distribution and concentration of iron in Bantu with siderosis.[57-59]

In a study of 44 Bantu at necropsy, in association with the pathologist, Dr. J. Higginson, it was reported that "iron storage occurs principally in the reticulo-endothelial system and the liver, and not until heavy deposits are present in this system does the element appear in the epithelial tissues." It was found that if cirrhosis was present, then the pathology picture was indistinguishable from that in idiopathic haemochromatosis, although a high concentration of iron in the spleen, almost paralleling that in the liver,

serves to distinguish between the two conditions. In very severe cases of siderosis, it was found that iron concentration in the liver reached 5 per cent, in the spleen, 10 per cent, and in vertebral bodies, 4 per cent, all on a dry weight basis. Subsequent investigations by other workers have led to not wholly unanimous conclusions, save that there is full agreement that in severe siderosis when cirrhosis is present, the histological picture presented is the same as that in classical haemochromatosis.

4. PATHOGENICITY OF SIDEROSIS.[57-59]

One worker, MacDonald, has recently summarised his view of the position as follows:-

> "Repeated experiments in animals in which iron has been given orally and parenterally, and in humans with increased tissue iron from oral and parenteral administration, equal to or exceeding the amounts found in haemochromatosis, demonstrate conclusively that iron does not cause fibrosis or cirrhosis."

Studies by South African workers, Isaacson, Seftel, Bothwell, and others, however, suggest that iron deposition may promote fibrosis and may also promote the development of haemochromatosis in Bantu diabetics.

The yield of knowledge from studies on animals, in relation, not only to the causation of siderosis, but also the factors influencing its extent and severity, has been disappointing. Not least, no experimental studies have been carried out in which a Bantu diet with its high iron content has been compared with (i) the same Bantu diet without high iron content, (ii) a European diet, (iii) a European diet supplemented with iron to conform in concentration to that of a Bantu diet, and (iv) a stock diet. It is unfortunate that the "Bantu diets" previously used experimentally, usually have consisted almost wholly of maize, moreover, the iron supplements incorporated and fed to animals

have afforded fantastically higher iron concentrations than such occurring in the Bantu diet. Finally, many stock diets contain an iron concentration as high or even higher than that obtaining in a siderotic Bantu diet, namely, about ~~0.2~~ 0.02 per cent Fe dry weight (i.e. 100 mg. Fe in 500 g. dry weight of foodstuffs); yet stock diets of this type do not produce abnormal iron deposition in experimental animals. Thus, differences in iron sensitivity and tolerance between animals and man detract from the value of ~~the~~ experimental studies and increase the caution required in the interpretation and extrapolation of such studies to man.

SUMMARY AND SUGGESTIONS FOR FUTURE RESEARCH.

1. As indicated previously, the standard of the research work adduced is judged on the papers submitted (published or in press). Hence, only a few brief additional remarks appear necessary.

2. The phenomenon of siderosis and its ramifications is fascinating on account of its local distribution and previously unsuspected pathogenesis. While there is little doubt that the high iron intake of the Bantu is the primary aetiological factor, further research is required on the nature and influence of promotive factors, e.g. frequency and intensity of exposure, state of nutrition, alcohol intake, etc. But the more important need facing research workers is to elucidate the pathogenicity of the phenomenon in the Bantu in relation to hepatic abnormality or disease, in relation to diabetes and idiopathic haemochromatosis, and also in relation to osteoporosis and scurvy.

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PART II CONTINUED.

STUDIES BEARING ON THE METABOLISM
OF IRON BY BANTU CHILDREN AND ADULTS.

COPIES OF PAPERS PUBLISHED OR IN PRESS.

Letter to the Editor
reprinted from THE LANCET, *April* 1, 1961, *pp.* 723-724

IRON-RETENTION DISEASES

SIR,—Your leading article [1] dealt primarily with the pathogenesis of siderosis in the South African Bantu. I question your views on the importance of the role either of previous hepatic damage or of malnutrition in causing siderosis. As propounder of the "iron overload" hypothesis of Bantu siderosis,[2 3] may I draw attention to a number of points.

(1) In the first place, your view of siderosis without qualification as a "disease" does not seem justifiable. Work locally [4–7] indicates that in a few siderotics the condition may cause or promote clinical disease (diabetes, cirrhosis); nevertheless, many observers have noted severe siderosis in Bantu livers with normal histology. Furthermore, in pioneer absorption studies, such as that of Widdowson and McCance,[8] many grammes of iron were retained; is it considered that the relevant subjects subsequently suffered from iron-retention "disease"? And are all those who have had their iron stores increased by blood-transfusion regarded as suffering from iron-retention "disease"?

(2) In a letter to your journal, I sought to point out that in all relevant studies carried out on man, a high iron intake leads to excessive absorption.[9] This is the normal response to high iron intake. Studies on whites have shown that with intakes at the levels reached, sometimes habitually, more often intermittently, by the Bantu, the iron retentions are sufficient to account quantitatively for the siderosis in them. There seems no reason to believe that non-whites are likely to respond differently from whites to the same intake. There is therefore no need to invoke previous liver damage or malnutrition as ætiological factors, although it is possible that they play an as yet undefined role in the development of the condition.

(3) Your leading article concludes that previous disordered hepatic metabolism could be primarily responsible for the excessive iron uptake from the undue amount present in the

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Bantu diet. But should the condition be due primarily to previous liver damage, there is no need to consider high iron intake as a contributory factor. In idiopathic hæmochromatosis there is no question of a high iron intake being implicated. Furthermore, admittedly, the Bantu certainly have a high incidence of hepatic fibrosis, though opinions differ on whether they have a higher incidence of cirrhosis. But plenty of other non-white populations have a high incidence of hepatic fibrosis and cirrhosis; can it be explained why such groups do not develop siderosis?

(4) Turning now to the malnutrition theory of Bantu siderosis—the theory implies widespread malnutrition among these people. But the Bantu have not the monopoly of dietary deficiencies. I have visited other parts of Africa, South Eastern Europe, the Middle East, and India, and would consider that, speaking generally, the South African Bantu are much more favourably nourished compared with many other peoples. If indeed malnutrition is implicated, why then is siderosis not almost universal? Incidentally, you quote Golberg and Smith [10] as believing that the low protein content of the Bantu diet may be the factor responsible, and state that the Bantu intake " is certainly less than the usually recommended daily minimum of 80–100 g. protein ". But the Johannesburg Bantu adult diet is *not* low in protein; moreover, your figure of 80–100 g. is far higher than that recommended by the various dietary standard bodies.[11] It is possible, as previously noted, that an iron-absorption lesion, secondary to malnutrition and liver damage, may play a deleterious role *only* when the iron intake is high.[2] But we have found serum-iron raised as high in Bantu population-groups with similar excessive iron intakes but greatly differing nutritional state.

(5) The malnutrition hypothesis suggests that nutritionally induced pancreatic dysfunction may promote siderosis in the Bantu.[12] I know of no evidence, histopathological or biochemical, of widespread pancreatic damage in the South African Bantu.

(6) A so-called " bad " human diet—in contrast to a " good " diet (stock diet)—has been shown experimentally to promote or cause siderosis in rats, especially when iron intake is high.[13] It is difficult to assess how, if at all, such studies bear on human siderosis. Quite apart from uncertainties inherent in extrapolating from animals to man, (a) the diet was not a Bantu diet; (b) the excessive iron concentration of the experimental diet was far greater than that of the diet consumed by the Bantu; (c) it is even questionable whether the rat is a suitable animal: the normal iron concentration of rat stock diets does

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not cause excessive iron retention in that animal, whereas the *same* concentration in human diets *does* cause abnormal retention of the element in man.

(7) Finally, Golberg and Smith,[10] as well as your leading article,[1] have hazarded views on the causation of Bantu siderosis, a condition involving excessive *intestinal absorption*, on the basis of experimental studies of *parenterally induced* iron overload. The soundness of such reasoning is open to question.

I do not by any means consider that we have all the the knowledge that we need for the full understanding of siderosis in the Bantu. But I submit, as I did ten years ago,[2] that there is sufficient evidence to explain the phenomenon in terms of excessive iron intake, and would repeat there is no need to invoke other factors. If hepatic damage and malnutrition do play significant roles, then there has surely been ample time for advocates to bring forward unequivocal supporting evidence.

South African Institute for
Medical Research, Johannesburg,
South Africa. ALEXANDER R. P. WALKER.

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Serum Iron and Iron-binding Capacity in the South African Bantu

EXCESSIVE amounts of iron are frequently present in various organs and tissues of adult South African Bantu[1]. Among these people, the iron intake is often high, as much as 200 mgm. per diem[2]. Further, occasional high values for serum iron have been reported among the Bantu of Bechuanaland[3]. In view of these facts, serum iron-levels, iron-binding capacity and other data have been determined in groups of adult Bantu from different regions of Southern Africa.

The Johannesburg group, of ages up to sixty years, were from a local non-European hospital; they were either on the staff or were suffering from complaints unlikely to influence levels of serum iron or iron-binding capacity. The Bantu males, 18–40 years, were workers from different territories, passed as medically fit for service in the gold mines. The European controls were members of the staff of this Institute.

Samples were taken by venipuncture between 9.30 and 11.30 a.m., the usual precautions being taken to prevent contamination with iron. Serum iron was determined using the thioglycollic acid method. The iron-binding capacity was determined by the method of Rath and Finch[4]. The total iron-binding capacity was obtained by adding the value

MEANS, STANDARD DEVIATIONS AND RANGES OF SERUM IRON AND TOTAL IRON-BINDING CAPACITY IN DIFFERENT BANTU GROUPS

	Remarks	Serum iron (γ per 100 ml.)	Total iron-binding capacity (γ per 100 ml.)
Bantu females	Johannesburg area	130 ± 40 (20)* (60–215)	335 ± 55 (17)* (240–435)
Bantu males	Johannesburg area	230 ± 75 (14) (110–380)	385 ± 50 (14) (320–475)
	Group *A*†	105 ± 45 (39) (15–225)	375 ± 70 (39) (225–590)
	Group *B*‡	285 ± 100 (68) (110–550)	520 ± 90 (42) (395–830)

* Number of subjects.

† Bantu with serum iron and total iron-binding capacity within normal range; Pondoland (13), N. Transvaal (Bapedi) (14), Tanganyika (12).

‡ Bantu with increased serum iron and total iron-binding capacity, significantly higher than those of group *A*; Mozambique (44), Angola (12), Nyasaland (12).

for serum iron to the iron-binding capacity. The difference between duplicates was never more than 10 per cent; all figures, therefore, including means and standard deviations, are given to the nearest 5 γ.

Our results for control groups of Europeans were in close agreement with values reported by other workers[4,5].

Several of the individual values obtained for serum iron and total iron-binding capacity were higher than any reported for such diseases as idiopathic hæmochromatosis or transfusional siderosis[4]. In no case has serum iron saturation been found. Further, among the Pondos and Bapedi examined, a few very low values for serum iron were obtained, which were, however, consistent with normal hæmoglobin levels.

Whether or not our groups with high serum iron and total iron-binding capacity values correspond with groups having high iron intakes, or displaying abnormal deposition of iron, is being investigated.

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TH. GERRITSEN
A. R. P. WALKER

Human Biochemistry Unit,
Council for Scientific and Industrial Research,
South African Institute for Medical Research,
Johannesburg.
Sept. 12.

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SERUM IRON LEVELS IN SIDEROSIS DUE TO HABITUALLY EXCESSIVE IRON INTAKE

BY J. HIGGINSON, K. J. KEELEY, M. ANDERSSON, AND A. R. P. WALKER

(From the Geographical Pathology Unit and the Human Biological Unit, Council for Scientific Research and Industrial Research, South African Institute for Medical Research, and the Baragwanath Non-European Hospital, Johannesburg, South Africa)

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Previous reports from South Africa have drawn attention to the heavy iron intake, and to the high frequency of hemosiderin deposition in the liver and other organs of the indigenous Bantu population (1, 2). In addition, observations in different Bantu population groups have demonstrated elevated levels of serum iron and total iron binding capacity in Bantu adults of both sexes. Saturation is very rarely observed in contrast to findings in idiopathic hemochromatosis (3). In view of these observations it was considered worth while to determine how far serum iron levels reflected the extent of siderosis in a hospitalized population group in this area. Since it is our experience that the severity of hepatic siderosis correlates well with the degree of visceral siderosis elsewhere in the body, the present paper represents our findings in a small series of patients in whom both liver biopsies and serum iron determinations were carried out.

MATERIALS AND METHODS

The liver material for this study came from 26 hospitalized Bantu patients (aged 17 to 66 years) in whom liver biopsies were carried out as necessary adjuncts to diagnosis. Since it was difficult to obtain livers in which siderosis was negligible, one six year old child with minimal siderosis (plus-minus) was added. There were 26 needle biopsies and one surgical biopsy in this series. In Table I, the diseases causing the admission of the patient to hospital are listed. It has been previously shown that there is no association of siderosis to any specific disease (1). The biopsies were examined by routine histopathological methods, but an additional section was stained for hemosiderin by Perl's reaction as described by Lillie (4).

Serum iron levels were determined as previously described (3). Patients in whom a viral hepatitis was suspected clinically were excluded in view of the alterations in serum iron levels known to occur in this condition. In all, a total of 27 subjects (14 males and 13 females) were available for study, but as the data obtained gave significant results it was considered unnecessary to extend the series.

Since these liver biopsies had been obtained for diagnostic purposes it was not possible to determine the degree of siderosis by chemical methods. The degree of hemosiderin deposition was therefore determined subjectively by one observer who was unaware of the serum iron levels. All biopsies were graded when first examined and again at the end of the study after re-staining in order that grading should be as uniform as possible. Siderosis was graded from 0 to 3 plus, according to the degree of hemosiderin deposition in the liver cells (fL) and Kupffer cells (fK), separately, and also according to the total liver deposits (fT). The portal tracts were not considered separately as previous experience indicated that deposits here were variable, being dependent on the degree of portal fibrosis.

RESULTS

The results obtained are summarized in Tables I and II. It will be observed that there is a significant correlation between mean serum iron levels and the presence or absence of siderosis in the liver, especially as determined by the degree of deposition in the Kupffer cells (fK) or in the liver as a whole (fT). The serum iron levels in cases in which the deposits are described as 0 or plus-minus were definitely lower than those in cases with heavily siderotic livers. It was observed, however, that once significant iron deposits were present in the liver no correlation was apparent between the degree of siderosis and mean serum iron levels. For statistical purposes, therefore, the 0 and plus-minus groups were grouped together as were also the 1 plus to 3 plus groups.

In no liver in which hemosiderin was absent (0), of which there were five in the series, did the serum iron levels rise above normal (180 μg. per cent) (Table I). On the other hand, in 3 of the 17 livers in which the iron deposits in the liver were graded 1 plus to 3 plus, the serum iron levels lay below 180 μg. per cent., *i.e.*, Patients 11, 18 and 19 (Table I).

In only one case in the current series was anemia

TABLE I

Serum iron levels, degree of hepatic siderosis, and primary disease causing admission of patient to hospital

Subject	Sex	Age	Disease	Serum iron μg. %	Degree of liver siderosis		
					fL	fK	fT*
1	F	34	Hypochromic anemia	64	0	0	0
2	F	22	Amoebiasis	88	0	0	0
3	M	28	Splenic vein thrombosis	136	0	0	0
4	F	30	Undiagnosed	149	0	0	0
5	M	21	Tuberculosis of spine	176	0	0	0
6	F	6	Malnutrition	60	+	±	±
7	M	36	Hilar lymphadenopathy	125	+	±	±
8	F	23	Chiari's syndrome	167	±	±	±
9	F	22	Pellagra and malnutrition	244	±	0	±
10	F	30	Gonococcal arthritis	264	+	±	±
11	M	47	Hepatic carcinoma	160	+	+	+
12	F	40	Obesity	201	+	+	+
13	F	60	Diabetes mellitus	274	+	++	+
14	F	18	Pellagra and malnutrition	444	+	+	+
15	M	48	Cirrhosis	243	++	++	++
16	F	34	Pellagra and malnutrition	304	+++	+	++
17	M	40	Pellagra and malnutrition	324	+	+++	++
18	M	64	Carcinoma of pancreas	120	++	+++	+++
19	F	43	Pellagra and malnutrition	123	+++	+++	+++
20	M	48	Cirrhosis	201	+++	++	+++
21	M	31	Tuberculous peritonitis	250	++	+++	+++
22	M	52	Pellagra and malnutrition	250	++	+++	+++
23	M	42	Diabetes mellitus	250	++	++	+++
24	M	35	Pellagra and cirrhosis	274	++	++	+++
25	M	43	Hypertension	385	+++	+++	+++
26	M	44	Pellagra and malnutrition	434	++	+++	+++
27	F	55	Congestive cardiac failure	490	+	+++	+++

* The discrepancy which sometimes exists between fT, fL, and fK is due to the fact that fT also takes into consideration the hemosiderin deposits in the portal triads.

TABLE II

Correlation of mean serum iron levels and degree of hepatic siderosis

Degree of siderosis*	Number of subjects	Serum iron, μg./100 ml.			"t"†
		Mean	Range	Standard deviation of mean	
A. In liver cells (fL)					
0 and ±	7	146.3	64–244	22.4	3.29
+ to +++	20	258.8	60–490	25.9	
B. In Kupffer cells (fK)					
0 and ±	10	147.3	60–264	21.8	3.82
+ to +++	17	278.1	123–490	26.4	
C. In total liver (fT)					
0 and ±	10	147.3	60–264	21.8	3.82
+ to +++	17	278.1	123–490	26.4	

* 0 = No hemosiderin deposits present. ± = Minimal hemosiderin deposits. + to +++ = Mild to severe hemosiderin deposits.

† Significance of difference between means calculated according to Hald (6).

of the iron deficiency type present. In this subject the serum iron level was 64 μg. initially at the time of the biopsy and hemosiderin was not demonstrated in the liver. When the degree of siderosis was doubtful (plus-minus), the serum iron levels were variable.

CONCLUSIONS

These findings indicate that high serum iron levels in hospital practice in this region are indicative of increased hemosiderin deposition in the liver of patients who are not suffering from disorders liable to cause elevation of the serum iron levels such as hepatitis, hemolytic anemia, and pernicious anemia in relapse. Occasionally, however, normal serum iron levels may be observed in cases with well marked siderosis. In two of the three siderotic cases with normal serum iron levels in the present series, the patients were seriously ill with advanced neoplastic disease. In view of the findings by Finch and Finch (5) that serum iron levels may fall in patients with hemochromatosis who develop liver carcinoma or severe infection, the probability that the normal serum iron levels in these two patients may be due to concomitant neoplasia must be considered

The data are insufficient to permit any conclusions regarding the probability of a low serum iron level being found in a siderotic liver.

SUMMARY

Serum iron levels and the severity of siderosis as determined by liver biopsy were correlated in a series of 26 South African Bantu adults and one child derived from a population known to be habituated to an excessively high iron intake. The correlation between mean serum iron levels and the degree of siderosis was highly significant if the patients were divided into groups with and without significant hepatic deposits. There was, however, no correlation between the serum iron levels and the severity of siderosis once significant iron deposition was present in the liver.

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CORRECTION OF HAEMATOLOGICAL DATA FOR ALTITUDE

SIR,—I would like to refer to Dr. H. Lehmann's abstract (*Trop. Dis. Bull.* 1956, **53**, 356) of a paper by Demaeyer, Chardome and Peel, entitled " Examination for parasites and variations in serum protein as functions of altitude, in Africans of the Katana-Lwiro area " (*Ann. Soc. belge Méd. trop.* 1955, **35**, 293).

Dr. Lehmann's abstract serves to focus attention on the present unsatisfactory state of knowledge concerning the precise alterations in blood values which occur with changes in altitude. The fact that haemoglobin concentration, haematocrit reading, and red cell count, rise with increase in altitude is not in dispute, but the lack of exact information is well reflected in the scant references made to the subject in standard textbooks on haematology. The reason for this neglect is not clear, when it is borne in mind that a by no means insignificant proportion of the world's population dwell at altitudes well above sea-level, particularly in India, China, and Africa.

In Johannesburg (5,700 ft. above sea-level), not to speak of the extensive highlands occupying much of Southern Africa, the subject of correction of values is particularly apposite. I am not a haematologist ; nevertheless, blood data on the Bantu, with the varying degrees of malnutrition and parasitism prevailing, are naturally of great interest to many of us who are engaged in investigating biochemical and metabolic problems on these people. The subject takes on added interest in view of their excessively high iron intake, which approaches and occasionally exceeds 200 mg. per diem (Walker, A. R. P., and Arvidsson, U.B. *Transactions*, 1953, **47**, 536). In the absence of knowledge of normal values for every 1,000 ft. rise in altitude, some means of calculating values to sea-level is indispensable for comparative purposes.

Before considering the quantitative side of the problem, some of the uncertainties in our knowledge should be appreciated. Thus —

(1) Is it valid to apply correction factors equally to all types of subjects — infants, children, men, women (pregnant and non-pregnant), and aged people ?

(2) With rise in altitude, are the relevant changes regularly proportional? And if this is the case, up to what altitude is this valid ?

(3) Are correction factors applicable to groups of subjects only, or also to individuals ?

(4) Regarding the time factor, is the adaptation to changes in altitude regular or irregular ?— does it take days, weeks, or months to reach a steady state ?

At this Institute, the following Table is used which provides data on normal haematological values for White adults at the altitude of the Witwatersrand (5,700 ft.). The data are those reported by Dr. H. I. Lurie (*Quart. J. exp. Physiol.* 1945, **33**, 91). Normal values at sea-level are also given.

Haemoglobin. The following Table indicates increases of 2.1 and 1.8 per cent. per 1,000 ft. for men and women respectively. Fitzgerald's Law allows for a rise of 10 per cent. in haemoglobin concentration per 100 mm. change in barometric pressure. The mean pressure in Johannesburg is about 625 mm., hence the rise per 1,000 ft. is approximately 2.4 per cent. The correction is greater than that derived from the Table, but I have used the

TABLE. Hamaetological data at sea-level and at the altitude of the Witwatersrand.

Haemoglobin g./%blood	Males	Females
Witwatersrand	15.3—17.7—20.2	12.9—15.3—17.8
Sea-level	14.0—15.8—18.0	11.5—13.9—16.0
Erythrocytes million/c.mm.		
Witwatersrand	4.87—5.6—6.31	4.2—5.0—5.71
Sea-level	4.6—5.4—6.2	4.2—4.8—5.2
Haematocrit %		
Witwatersrand	44—50—56	39—45—51
Sea-level	40—47—54	37—42—47

The three figures given in a line signify, the first the lower limit of a 95 per cent. range, the second the mean, and the third the upper limit of the 95 per cent. range.

Fitzgerald factor in a number of publications, preferring that my values corrected to sea-level are unfavourably biased, rather than the reverse. It is clear that the factors given are not applicable at very high aititudes, as is indicated in certain studies quoted in Lurie's paper.

Red Cell Count. Mean values given in the Table are very similar to those reported for Indian adults at a similar altitude (Da Gupta, C. R., *Indian med. Gaz.*, 1952, **87**, 95), namely, 5.49 and 5.02 millions per c.mm. for males and females respectively. Other comparable Indian studies give lower values. According to the Table, the rise in red cell count is approximately 0.70 per cent. per 1000 ft. This figure is considerably lower than that indicated in the figures given in the example cited by Dr. Lehmann, which shows an almost 5 per cent. change per 1,000 ft.

Haematocrit. According to the Table, the elevation in packed cell volume is about 1.1 per cent. per 1,000 ft. rise in altitude. The mean values cited are proportionally in harmony with data given for White adults at Salt Lake City, which is 4,250 ft. above sea-level (Wintrobe, M. M. *Clinical Haematology*, 3rd. Ed. London : Kimpton, 1951).

Briefly, then, it would seem that with increasing altitude, elevations in haemoglobin concentration are appreciable, while elevations in haematocrit readings and red cell count, particularly the latter, are slight.

As noted before, the reason for the lack of satisfactory data in this field is not clear, although it is highly probable that valuable data are already at hand, but remain unpublished.

In the light of the foregoing, provided one is aware of the limitations and uncertainties attached to correction factors, it is considered that their present use is certainly justified, at least at altitudes several thousand feet above sea-level.

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A. R. P. WALKER.

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SERUM IRON AND IRON-BINDING CAPACITY IN THE BANTU

TH. GERRITSEN, D. PHIL. (UTRECHT) AND A. R. P. WALKER, PH.D. (CAPE TOWN)

Human Biochemistry Unit

South African Institute for Medical Research, Johannesburg

South African Council for Scientific and Industrial Research

The iron metabolism picture of the South African Bantu is unusually interesting for the following reasons: (1) Their iron intake is often very high, sometimes as much as 200 mg. per diem, derived not only from the element present in their customary diet, but also from adventitious iron taken up from iron utensils during the preparation of food.[1] (2) At necropsy, excessive deposition of iron (siderosis) is frequently seen in the tissues of adult Bantu.[2, 3, 4] (3) Hypochromic anaemia is extremely rare.[5] (4) Abnormally high serum iron (S.I.) levels have been reported among Bechuana Bantu.[6]

Briefly, our desire is to find out whether there is any correlation between iron intake, certain blood values—S.I., total iron-binding capacity (T.I.B.C.) and haemoglobin concentration (Hb.)—and the incidence of siderosis in various Bantu groups. If such a correlation exists it would permit the presence of siderosis to be determined in living people of all age groups, and thus facilitate the investigation of the geographical distribution of the phenomenon. This approach would be a considerable advantage, since obviously determination of the distribution by obtaining liver biopsies, or the use of visceratomes as suggested by Davies and Trowell,[7] is not justifiable.

Kooyman [8] has stated that high S.I. does not necessarily correlate with high iron stores. But no S.I. investigations have yet been undertaken on patients who have had their total iron stores determined at necropsy. In advanced haemochromatosis and transfusional siderosis, iron stores are known to be very high.[9, 10, 11] In these diseases, an increased S.I. is usually observed, and as the T.I.B.C. remains normal, saturation almost complete, or complete, of the iron-binding protein in the serum (called transferrin by Laurell [12]) is found.[13, 14]

Abnormal deposition of iron in the tissues of the Bantu is known to reach levels at least as high as in the two diseases mentioned.[3, 9, 10, 11] From a *priori* considerations, one would anticipate that elevated S.I. and saturation levels would be observed among these people; however, no alterations would be expected in T.I.B.C. Determination and discussion of these values in the Bantu, some of which have been summarized briefly elsewhere,[15] form the substance of this paper.

MATERIALS

The majority of our subjects were newly recruited Bantu mine labourers, accepted as medically fit; they were investigated immediately upon arrival at the Witwatersrand Native Labour Association Headquarters in Johannesburg. They came from Northern Transvaal (Bapedi, 14), Pondoland (21), Swaziland (12), Tanganyika (12), Basutoland (12), Zululand (12), Mozambique (44), Angola (12) and Nyasaland (12). Their ages were from 17 to 40 years. There was also an adult male group from the Johannesburg area (14), composed of 12 out-patients, attending the non-European Department of the Johannesburg Hospital, and 2 subjects working at this Institute. To obtain 'normal average' values (see *Discussion*) for comparison with the Bantu results, 15 European subjects, 9 men and 6 women, from this Institute, whose ages ranged from 21 to 56 years, were investigated. Twenty-three Bantu women were also studied, this group being comprised of 9 nurses from the Baragwanath non-European Hospital at Johannesburg, and 14 out-patients from the same hospital or from the non-European Department of the Johannesburg Hospital, who had had minor surgical treatment. Their ages ranged from 18 to 56 years.

METHODS

Bloods were collected by venipuncture between 9 a.m. and 10.30 a.m. Specially cleaned and greased 20 ml. syringes were used. These and all other glassware were thoroughly cleaned to avoid iron contamination.

S.I. determinations were carried out using the thioglycollic acid method [16]; a Hilger Spekker absorptiometer (Ilford Filter 603) was employed for the colorimetric measurements.

Iron-binding capacity (I.B.C.) was determined by the method of Rath and Finch.[13] The T.I.B.C. was calculated by adding the S.I. value to the I.B.C.; the percentage saturation was obtained by dividing S.I. × 100 by the T.I.B.C.

When the amount of serum was sufficient (about 75% of cases), determinations were done in duplicate. The average difference between duplicates in S.I. determinations was 8γ/100 ml. serum; for I.B.C. this figure was 15γ.

Hb. determinations were carried out by the oxyhaemoglobin method; for the colorimetric measurements a Hilger Spekker absorptiometer (Ilford Filter 602) was used, the instrument being standardized by determinations of total iron in blood.

RESULTS

The results are tabulated as follows. Table 1 gives the values for European men and women. As it would require too much space to give all Bantu results in detail,* only the values for the Pondos and the Nyasis, being examples of a group with low average values and with high average values, respectively, are given in Tables 2 and 3. In Table 4 are given means, standard deviations, and ratios to the 'normal average' values, for S.I., T.I.B.C., and percentage iron saturation for all groups investigated. Table 6 gives Hb. values for the various adult male groups.

DISCUSSION

Many workers appear to be unaware of the wide range in S. I. level, which obviously must be borne in mind in interpreting results in this field. As Høyer pointed out in 1944.[17] any individual can have an enormous variation in S.I., not only in the course of the day, but also on different days. He considers that daily differences of up to 60γ per 100 ml. serum must be regarded as normal. On this account we maintain that a single S.I. determination

* Detailed results are available on request.

TABLE 1

Serum iron, total iron-binding capacity, and percentage iron saturation in European subjects.

No.	*Sex*	*S.I.* γ/100 *ml.*	*T.I.B.C.* γ/100 *ml.*	*% sat.*
1	f	105	345	30
2	f	185	365	51
3	f	130	410	32
4	f	90	270	33
5	f	90	260	35
6	f	70	355	28
Average	f	112	334	35
7	m	125	380	33
8	m	155	335	46
9	m	70	295	24
10	m	110	330	33
11	m	110	380	29
12	m	95	320	30
13	m	100	300	33
14	m	120	320	37
15	m	145	360	40
Average	m	114	335	34
Total Average	..	113	335	34

TABLE 2

Serum iron, total iron-binding capacity, percentage iron saturation and haemoglobin values in Bantu men from Pondoland.

No.	*S.I.* γ/100 *ml.*	*T.I.B.C.* γ/100 *ml.*	*% sat.*	*Hb.* g. %
1	30	315	10	18·7
2	155	380	41	18·8
3	95	345	27	16·6
4	70	320	22	17·4
5	200	465	43	15·8
6	20	255	8	18·0
7	15	225	7	17·8
8	130	375	35	17·4
9	145	405	36	16·6
10	80	360	22	16·9
11	85	285	30	17·2
12	165	435	38	17·9
13	120	340	35	18·0
14	40	285	14	17·8
15	210	275	76	16·5
16	25	365	7	17·2
17	35	325	11	17·2
18	65	355	18	16·5
19	195	350	56	21·5
20	110	320	34	16·4
21	100	325	31	18·2
Average	100	338	29	17·6

on a patient is of very little value. Only an average for a group is informative, and even in this respect, one is only entitled to regard a difference between 2 groups as being significant when blood samples are taken at the same time of the day. All our blood samples were collected between 9.0 a.m. and 10.30 a.m.

In our comparatively small group of Europeans (6 men and 9 women) we found no difference between average values for the 2 sexes, for S.I., T.I.B.C. and percentage saturation. Pirrie,[18] however, who has reviewed the literature on this subject up to 1952, reported that 8 out of

TABLE 3

Serum iron, total iron-binding capacity, percentage iron saturation and haemoglobin values in Bantu men from Nyasaland.

No.	*S.I.* γ/100 *ml.*	*T.I.B.C.* γ/100 *ml.*	*% sat.*	*Hb.* g. %
1	530	790	67	18·9
2	175	500	35	18·7
3	340	640	53	18·2
4	550	590	93	18·2
5	260	450	58	—
6	155	395	39	18·6
7	430	830	52	18·5
8	290	600	48	17·4
9	380	520	73	17·8
10	370	480	77	18·5
11	320	510	63	18·7
12	520	780	67	19·1
Average	360	591	60	18·4

10 groups of workers found a significant difference in S.I. between values for males and females. Only Cartwright and Wintrobe, investigating an American group,[19] and Brøchner-Mortensen and Olsen,[20] studying a Scandinavian group, found the difference in S.I. too small to be significant. Hence, our 'normal average' figures, which we require for statistical comparison with Bantu data, include both European males and females.

As mentioned previously, in advanced haemochromatosis and transfusional siderosis, where iron stores are known to be large, saturation of the transferrin is usual, i.e. the S.I. level increases up to the T.I.B.C. value, which, however, remains unaltered. The T.I.B.C. is reported to rise only in late pregnancy (observed in Bantu [21] as well as in European [22, 23] subjects), and possibly in patients suffering from iron-deficiency anaemia.[13] We found elevated S.I. values in 5 groups, viz. from the Johannesburg area, Zululand, Mozambique, Angola, and Nyasaland (see Tables 4 and 5); and surprisingly the T.I.B.C. showed significant elevations in the last 3 groups. Further, in no case was 100% saturation of the transferrin found. This picture, then, of elevated T.I.B.C. values and unsaturation of the transferrin, constitutes a salient point of difference between what is observed in the Bantu and what occurs in advanced haemochromatosis and transfusional siderosis.

As we have already reported,[15] in 2 tribal groups (Pondos and Bapedi) we found some very low S.I. values (see Table 2, subjects No. 1, 6, 7, 14, 16 and 17). The Bantu concerned, however, had normal or even high Hb. levels. Although low values are occasionally associated with iron-deficency anaemia,[13] evidently this was not the case with these subjects.

In considering the Hb. values (Table 6) it must be borne in mind, firstly, that the altitude of the Witwatersrand is 5,000 to 6,000 feet; and secondly, that our subjects came from mainly lower-lying regions. Among all Bantu examined, who, incidentally, were wholly unselected from very large groups, not one subject was anaemic. No correlation was apparent between S.I. and Hb., and between T.I.B.C. and Hb. The values obtained in this series, and on further subjects, will be discussed in a subsequent paper.

The question arises as to how far the information gained in this investigation fulfils the aims set out in the introduction. With regard to iron intake, we have only the information given by the subjects themselves, and this information largely dealt with whether iron or clay pots, or both are used for the preparation of foods. The Angola group maintained that they were fond of fermented cereal products, and consumed much of these, and that iron vessels were commonly used for their preparation; these people gave very high values for S.I. and T.I.B.C. On the other hand, the Nyasis assured us that iron pots were not used, yet this group has the highest S.I. and T.I.B.C. values yet reported in the literature. Until more accurate information is available on actual iron intakes, no attempt can be made to determine whether a correlation exists between iron intake and the above serum values.

Next, in regard to serum values and the presence of abnormally high iron stores, there is ample evidence that about half of the Bantu males coming to necropsy in Johannesburg show abnormally high iron deposits in the viscera.[3, 4] In this respect our group of 14 Johannesburg males gave a significantly elevated average S.I. value. On the other hand, Strachan found siderosis to be very common among the Basuto,[2] yet our average value for Basuto males was only 123γ per 100 ml. serum.

From these considerations two points are apparent. Firstly, to obtain accurate data on the habitual iron intake of regional Bantu groups it is essential to visit them, to study local dietary habits, to collect samples of prepared foodstuffs, and, whenever possible, to determine iron concentration on post-mortem material. It appears essential, moreover, to undertake determination of S.I. and T.I.B.C. on such people in the field. This latter point arises from the fact that we have found differences in average S.I. values in Swazi mine labourers examined in Johannesburg, and Swazi adult males examined in Swaziland. On this account, we can not be certain that our tribal groups of mine labourers are representative of the corresponding population of their regions of origin. It is certainly conceivable that a component as labile as S.I. can be markedly affected by dietary and other changes occurring between the time of leaving home and being examined in Johannesburg—sometimes a matter of days.

TABLE 4

Means, standard deviations, ranges, and ratios to 'normal average' European values, of serum iron, total iron-binding capacity and percentage iron saturation in the Bantu groups investigated.

Group	*Area*	*Serum iron (γ per 100 ml.)*			*Total iron-binding capacity (γ per 100 ml.)*			*% iron saturation*		
		No. of subjects	*mean values and range*	*ratio**	*No. of subjects*	*mean value and range*	*ratio**	*No. of subjects*	*mean value and range*	*ratio**
European men and women		15	113±31 (70—185).	—	15	335±42 (260—410)	—	15	34±7 (25—51)	—
Bantu women	Johannesburg area	20	129±39 (60—215)	1·1	17	336±56 (240—435)	1·0	17	37±7 (25—50)	1·1
Bantu men	Johannesburg area	14	229±77 (110—380)	2·0	14	385±49 (320—475)	1·2	14	59±16 (34—92)	1·7
,, ,,	N. Transvaal (Bapedi)	14	98±46 (35—225)	0·9	14	378±62 (285—475)	1·1	14	26±13 (11—61)	0·8
,, ,,	Pondoland	21	100±62 (15—210)	0·9	21	338±57 (225—465)	1·0	21	29±17 (7—76)	0·9
,, ,,	Swaziland	12	110±43 (50—185)	1·0	12	345±34 (305—410)	1·0	12	32±13 (16—55)	0·9
,, ,,	Tanganyika	12	120±43 (65—225)	1·1	12	411±85 (240—590)	1·2	12	29±7 (21—42)	0·8
,, ,,	Basutoland	12	123±23 (90—155)	1·1	12	309±48 (270—400)	0·9	12	40±7 (28—52)	1·2
,, ,,	Zululand	12	158±48 (110—260)	1·4	12	400±44 (335—465)	1·2	12	39±10 (27—56)	1·1
,, ,,	Mozambique	44	264±94 (110—490)	2·3	19	450±56 (375—575)	1·3	19	56±13 (38—80)	1·6
,, ,,	Angola	12	294±95 (160—445)	2·6	11	559±76 (430—680)	1·7	11	54±12 (39—74)	1·6
,, ,,	Nyasaland	12	360±124 (155—550)	3·2	12	591±142 (395—830)	1·8	12	60±16 (35—93)	1·8

* Ratio obtained by dividing the value concerned by the mean value for the European group.

TABLE 5

Significances of differences* in serum iron, total iron-binding capacity and percentage iron saturation, between the 'normal average' European group and 10 groups of male adult Bantu.

Group from	*S.I.*	*T.I.B.C.*	*Percentage iron saturation.*
Johannesburg area ..	P<0·01	not signif.	P<0·001
N. Transvaal (Bapedi)	not signif.	,, ,,	not signif.
Pondoland	,, ,,	,, ,,	,, ,,
Swaziland	,, ,,	,, ,,	,, ,,
Tanganyika	,, ,,	,, ,,	,, ,,
Basutoland	,, ,,	,, ,,	,, ,,
Zululand	P<0·01	,, ,,	,, ,,
Mozambique	P<0·01	P<0·001	P<0·001
Angola	P<0·01	P<0·001	P<0·001
Nyasaland	P<0·001	P<0·001	P<0·001

* The statistical calculations have been done according to Fisher, R.A., *Statistical Methods for Research Workers*, London (1948).

TABLE 6

Haemoglobin values (means and ranges) for the various adult Bantu groups.

Group	*Mean Hb. g. %*	*Range Hb. g. %*
Women, Johannesburg area ..	15·5	12·0—17·6
Men, Johannesburg area ..	16·6	15·0—18·5
,, (Bapedi) N. Transvaal ..	16·9	15·5—18·7
,, Pondoland	17·6	15·8—21·5
,, Swaziland	17·0	15·2—18·6
,, Tanganyika	17·4	15·2—19·4
,, Basutoland	15·5	14·1—17·3
,, Zululand	17·0	15·3—18·4
,, Mozambique	15·4	11·2—19·4
,, Angola	17·4	15·9—19·4
,, Nyasaland	18·4	17·4—19·1

This aspect is being investigated further. The second point is that it is impossible to determine whether a direct correlation exists between serum values and siderosis, until we are able to undertake determination of S.I. values on Bantu known from liver biopsy studies to be siderotic. We are slowly accumulating data gained in the field on iron intake and serum values, and these will be presented in a further publication. We have also commenced to determine serum values in Bantu patients who have had liver biopsies carried out for diagnostic purposes; such information will necessarily take a long time to collect, since it can be gained only as opportunity offers.

Finally, we consider that our finding of elevated serum values in various Bantu groups provides a further aspect of abnormality in the iron metabolism picture of these people. The extent to which this aspect and the other aspects mentioned in the introduction are inter-related is not yet established.

SUMMARY

The iron metabolism picture in the Bantu is interesting on account of their unusually high iron intake, the frequent occurrence of siderosis, the rarity of hypochromic anaemia, and the elevations of serum iron levels and total iron-binding capacity which are occasionally observed.

This paper deals with levels of serum iron, total iron-binding capacity, and haemoglobin, in groups of young adult Bantu mine labourers from different regions in Southern Africa. In some groups, values for serum iron are higher than any yet reported, including the high values very frequently found in diseases such as haemochromatosis and transfusional siderosis. Also, in certain groups, elevations of total iron-binding capacity have been found, an unusual and unexpected finding. The latter observation, associated with unsaturation of the iron-binding protein in the serum, constitute a salient difference between what is observed in some Bantu, and in the two diseases mentioned. An interesting finding is the high average Hb. level for all groups studied.

Present knowledge is inadequate to allow us to determine whether a correlation exists between abnormally high values in the serum, and (a) habitual level of iron intake, and (b) incidence of siderosis.

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Haemoglobin Production in Grossly Undernourished African Bantu

[*To the Editor of the* BRITISH MEDICAL JOURNAL]

SIR,—From a comprehensive review of haemopoiesis in gross undernutrition, Keys and co-workers[1] concluded: "The evidence is overwhelming that anaemia develops during prolonged periods of caloric restriction, and the degree of anaemia appears to be related to the extent of the starvation. The anaemia . . . is not of the iron deficiency type." In the M.R.C. publication on *Studies of Undernutrition, Wuppertal, 1946–9*, Sherlock and Walshe[2] noted diminished blood volumes and low concentrations of haemoglobin, with deposition of iron in certain organs. They stated: "Since the haemoglobin in the blood stream is below normal levels, it is uncertain why the stored iron is not used for the manufacture of new haemoglobin. It has been suggested that the intake of dietary protein may be too low to allow the production of sufficient globin, but there is no concrete proof of this."

In the adult South African Bantu the iron picture is characterized by extremely high iron intakes (as much as 200 mg. per day), by elevated values for serum iron and total iron binding capacity, and by excessive deposition of the element in the viscera and other tissues, such deposition being present in about half of the urban adults examined at necropsy.[3] An interesting question thus arises regarding the haemoglobin levels of Bantu adults when grossly malnourished or undernourished. Do the high iron reserves act as a "brake" on the depression of values to be expected from severe deprivation of calories and other nutrients? Or, since the anaemia of undernutrition is not believed to be of the iron deficiency type, do low haemoglobin levels occur despite iron "overload"? To throw light on this issue, records were examined of 35 men and 21 women, these subjects being among the most severely undernourished and malnourished patients (25–50% under-weight) seen at Baragwanath Non-European Hospital (1,350 beds) during the last three-year period. Among these patients "pure" undernutrition was rare; three quarters were suffering from pellagra. Mean haemoglobin values, standard deviations, and ranges, after correction for the altitude of Johannesburg

(5,700 ft.—1,740 m.), for the 35 men were 12.1 ± 1.2, range 7.0–15.2 g.%; 37% of the patients had values of 14.0 g.% or more; for the 21 women, 11.1 ± 0.8, range 6.0–15.2 g.%; 48% of the patients had values of 12.0 g.% or more. Mean values are certainly higher than would be expected from the patients' clinical state. Thus, under the special dietary conditions which cause iron reserves to be unduly high, severe dietary privation need not lead to unduly low haemoglobin levels. In more than a third of the patients haemoglobin values lay within normal limits; hence one of two alternatives would appear to be valid. Either the present importance attached to haemopoietic factors other than iron is exaggerated, or the amounts of the other factors required are smaller than is usually believed, because they must have been contained in sufficient amounts in the Bantu patients' meagre diet, which had been consumed in most cases for several months previously. Details of this and related studies will be published elsewhere.—I am, etc.,

Johannesburg. A. R. P. WALKER.

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HAEMOGLOBIN CONCENTRATION AND NUTRITIONAL STATE IN SOUTH AFRICAN BANTU HABITUATED TO A VERY HIGH IRON INTAKE

A. R. P. WALKER, M.Sc., PH.D.

The Human Biochemistry Unit of the South African Institute for Medical Research, Johannesburg, and the South African Council for Scientific and Industrial Research

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A. R. P. WALKER, M.Sc., PH.D.

The Human Biochemistry Unit of the South African Institute for Medical Research, Johannesburg, and the South African Council for Scientific and Industrial Research

Haemoglobin concentration is often regarded as a useful criterion in the assessment of nutritional state.[1] The correlation, however, is not invariable, one important exception occurring when there is a high intake of iron, whether administered therapeutically, prophylactically, or involuntarily, as with the South African Bantu, whose habitual diet is exceptionally rich in iron.[2, 3] The purpose of this paper is to present and discuss evidence bearing on high iron intake, haemoglobin concentration, and nutritional state, with particular reference to local studies undertaken on the Bantu. Before describing these studies, the chief features of their iron-metabolism picture will be mentioned. Briefly (1) The iron intake is often unusually high, sometimes as much as 200 mg. per diem. It is derived not only from the element present originally in their customary diet, but mainly from adventitious iron taken up from iron utensils during the preparation of food, particularly acid fermented cereal products (pH 2—3).[2, 3] (2) Abnormally high values for serum iron are occasionally encountered in adults.[4] Our studies have revealed individual values for serum iron and total iron-binding capacity higher than any reported in the literature, including values occurring in idiopathic haemochromatosis and transfusional siderosis.[5, 6] (3) Hypochromic anaemia is extremely rare.[7] (4) At necropsy, abnormal deposition of iron is frequently seen in the tissues of adult Bantu: as much as 10 and 5% iron (dry weight) have been found in spleens and livers respectively.[8-10]

The studies carried out on the Bantu will now be presented.

MATERIAL AND METHODS

Subjects: Adult Males (Table 1).

Bantu mine workers. Groups I-III were Bantu mine workers who had come from various regions in Southern Africa. They were aged 18-40 years, and were medically fit; this state, however, must not be taken to imply freedom from venereal infection or parasitic infestation. They were known to be or suspected of being used to a high iron intake. They were examined at the Witwatersrand Native Labour Association Headquarters

in Johannesburg, the clearing station through which pass over 300,000 workers annually before proceeding to the different mining centres.

Group I was comprised of a mixture of tribal types. Values on these subjects were determined in the course of serum iron studies.[5, 6]

Group-II subjects, Barotse from Northern Rhodesia, came from an area where hookworm infestation is severe and widespread. Workers were examined during an investigation for quantitative data on blood loss and worm load in *ancylostomiasis* by means of a radio-active iron method.[11]

Group-III subjects, Shangaans from the border of Portuguese East Africa and Eastern Transvaal, were examined mainly during an investigation to determine blood loss and egg load in intestinal bilharzia (*schistosomiasis mansoni*).[12] A sub-group of Shangaans (not the same individuals) were examined after 15 months' service.

Bantu farm labourers. Group IV was composed of Shangaans who were investigated in a study parallel to the previous one (Group III).[12] Their blood was sampled in their home area in the valley of the Crocodile River in Eastern Transvaal, a region where 100% infestation with both forms of bilharzia, *S. haematobium* and *mansoni*, occurs.[13] Detailed clinical data on these subjects were not available.

Grossly malnourished hospitalized Bantu men. Group V included men admitted to Baragwanath Non-European Hospital (1,350 beds), near Johannesburg, suffering from gross malnutrition and, usually, pellagra. Full clinical and biochemical data were available.[13a] All subjects came from areas where a high iron intake was common.

Subjects: Adult Females (Table II).

Bantu farm labourers. These subjects, Group I, corresponded to Group-IV adult males.

Peri-urban Bantu women, pregnant and non-pregnant. These subjects (Group II) had been investigated to learn of the effect of habitually high iron intake on certain blood values in pregnancy.[14] Detailed clinical data were not available.

Grossly malnourished hospitalized Bantu women. These patients, Group III, corresponded to Group-V hospitalized men.[13a]

Healthy Bantu women. Group IV were healthy hospital nurses, full clinical and biochemical data being available. Approximately half were recruited locally, and the remainder were from different parts of the Union. They were divided into 2 sub-groups, those whose haemoglobin level had been determined on joining the staff, and a different series of nurses examined after at least a year's service.[15] All had come from areas where a high iron intake is known to be common.

Diet

Speaking generally, the staple sources of calories among the Bantu of Southern Africa are maize, wheat and, in certain areas, 'kaffir corn'

(sorghum), together with small amounts of legumes such as 'cow peas' (*Vigna unguiculata*), 'sugar beans' (*Phaseolus vulgaris*), and 'Jugo beans' (*Voandzeia subterranea*). Small, though very variable amounts of meat, milk, fruit and vegetables and sugar, are also consumed. The principal traditional drinks are 'marewu' and kaffir beer; these are fermented cereal preparations, consumed in large amounts, sometimes daily. Speaking generally, the diet is usually satisfactory in energy value (except occasionally between harvests for the rural dwellers), possibly adequate in gross protein, though low in animal protein, and low in fat. As noted previously, the iron intake is abnormally high, occasionally exceeding 200 mg, per diem.[2, 3]

Method of Haemoglobin Determination

In all cases, values were determined on venous blood by the oxyhaemoglobin method, using a Hilger Spekker Spectrophotometer (Ilford filter 602) calibrated against total iron determinations in blood.

RESULTS

The results are summarized in Tables I and II.

DISCUSSION

Comments on experimental observations

Bantu mine labourers. Bloods from Groups I-III subjects were withdrawn and examined in Johannesburg, the altitude of which is higher than the regions of origin of the subjects. Since bloods were taken immediately after arrival it is doubted whether the haemoglobin values found differ significantly from those obtaining at their home level. The averages for these medically-fit groups compare satisfactorily with the overseas mean value cited for healthy subjects. Among the Barotse examined (Group II), hookworm was common; the haemoglobin concentrations thus contrast with the low values so frequently noted in another hookworm area—Uganda—where hypochromic anaemia is very common, but where the iron intake is not unusually high.[19, 20] It will be observed that, after correcting for altitude, the mean haemoglobin value for the Shangaans (Group III) upon starting work on the gold mines did not differ significantly from the mean value found for another group of similar subjects 15 months later. Evidently, haemoglobin concentration was such that it could not be improved by the excellent diet provided by the mines.

Bantu farm workers. The clinical state of these workers was not known. However, in a few individuals who clinically appeared to be unusually healthy, or who seemed to be not enjoying good health, observations revealed no correlation between such impressions and subject's haemoglobin level. Mean values are satisfactory despite 100% bilharzial infestation.

Pregnant Bantu women. These subjects, with their involuntary iron

TABLE I. HAEMOGLOBIN LEVEL, NUTRITIONAL STATE, AND OTHER DATA ON BANTU ADULT MALES

Subjects	*Region of Origin*	*State of Health*	*No. of Subjects*	*Approximate Ht. above sea level (ft.)*	*Mean Hb. Conc., S.D. and range*	*Mean Hb. Conc. corrected to sea level**
Gr. I	Bapedi, N. Transvaal ...	Medically fit	14	3,500	16·9± 0·8 (15·5—18·7)	15·5
Bantu mine workers	Pondoland		21	0-4,000	17·6± 0·9 (15·8—21·5)	16·2
18-40 years	Swaziland		12	4,000	17·0± 1·0 (15·2—18·6)	15·4
	Tanganyika		12	2,000	17·4± 1·1) (15·2—19·4)	16·0
	Basutoland		12	4,000	15·5± 0·9) (14·1—17·3)	14·0
	Zululand		12	0-2,000	17·0± 0·9 (15·3—18·4)	16·3
	Moçambique		44	0-1,000	15·4± 1·2 (11·2—19·4)	15·2
	Angola		12	3,000-4,000	17·4± 1·0) (15·9—19·4)	15·9
	Nyasaland		12	3,000	18·4— 0·5 (17·4—19·1)	17·1
Gr. II Bantu mine workers 18-40 years	Barotse, Northern Rhodesia	Medically fit	120	3,000	16·2± 1·4 (11·9—18·1)	15·1
Gr. III Bantu mine workers 18-40 years.	Shangaans. Transvaal—Moçambique border.	Medically fit: data obtained on arrival.	96	1,000	15·2± 1·5 (12·9—17·9)	14·6
		Ditto, but different group: data after 15 months on mines diet.	65	5,500	16·3± 1·3 (13·0—18·0)	14·3
Gr. IV. Bantu farm labourers 20-55 years.	Shangaans— Eastern Transvaal ...	No clinical examination. Up and about workers. 100% infestation with *Schistosomiasis haematobium* and *mansoni*.	43	1,000	15·3± 1·5 (11·9—19·8)	14·7
Gr. V. Bantu urban men, 20-60 years.	Mixed Bantu, Johannesburg	Grossly malnourished hospitalized patients suffering severely from pellagra.	29	5,500	15·0± 1·2 (8·0—17·2)	13·1
White men		Healthy subjects	—	5,500	16·64[16] 17·76[17]	16·0±2·0[18]

TABLE II. HAEMOGLOBIN LEVEL, NUTRITIONAL STATE, AND OTHER DATA ON BANTU ADULT FEMALES

Subjects	*Region of Origin*	*State of Health*	*No. of Subjects*	*Ht. above sea level (ft.)*	*Mean Hb. Conc. S.D. and range*	*Mean Hb. Conc. corrected to sea level**
Gr. I						
Bantu farm labourers, 21-48 years.	Shangaans—Eastern Transvaal	Not clinically examined. 100% infested with *Schistosomiasis haematobium* and *mansoni*.	40	1,000	13·3± 1·5 (10·6—15·8)	12·8
Gr. II						
Bantu housewives 17-38 years	Mixed Bantu peri-urban near Pretoria.	Not clinically examined. Representative of peri-urban women	Non-pregnant 48	4,500	13·9± 0·9 (12·3—16·0)	12·5
			Preg. 1st half period 43		13·9± 0·9 (12·2—15·9)	12·5
			Preg. 2nd half period 49		13·7± 1·1 (11·8—17·3)	12·3
Gr. III						
Bantu urban women 33-61 years.	Johannesburg mixed population.	Grossly malnourished suffering severely from pellagra.	21	5,500	13·9± (7·0—16·6)	12·1
Gr. IV.						
Bantu nurses, 18-26 years.	Johannesburg mixed population.	Healthy Bantu nurses: on admission	102	5,500	14·7± 0·9 (11·1—17·1)	12·9
		after 1 year	54	5,500	15·3± 0·7 (13·3—17·8)	13·4
White women		Healthy subjects	—	5,500	14·43[16] 15·33[17]	14·0±2·0[18]

*According to Fitzgerald's Law,[17] haemoglobin concentration rises by 10% in 100 mm. fall in barometric pressure; this approximates to an elevation of 2·4% per rise of 1,000 ft. Although we have employed this correction factor, we must point out that, as far as we are aware, no relevant comprehensive long-term study has been undertaken on groups of individuals rising from sea level to 5,500—6,000 ft. and *vice-versa*.

prophylaxis, showed no fall in haemoglobin concentration as pregnancy progressed, in contrast to the depression normally observed.[18] Adequate clinical data were not available, but in a few women considered by the clinic medical officer to be enjoying good health, or to be displaying various stigmata of malnutrition, state of health showed no correlation with haemoglobin level.

Grossly malnourished hospitalized Bantu adults. The mean haemoglobin concentration of the sick men (after correcting for altitude), namely 13·1 g.%, lies below normal limits, i.e., 14-16 g.%. The corrected value for the sick women, namely 12·1 g.%, lies within normal limits, i.e., 12-14 g.%. Both means, of course, are significantly less than the corresponding values for medically-fit Bantu mine-workers (Group III, Table I), and the healthy Bantu nurses (Group IV, Table II) respectively. The salient finding is that the macrocytic anaemia which is so frequently a feature of malnutrition and undernutrition,[21] and the anaemia so often seen in pellagra, [1, 22, 23] did not characterize the patients. From a comprehensive review of haemopoiesis in gross undernutrition, Keys and his co-workers[21] concluded: 'The evidence is overwhelming that anaemia develops during prolonged periods of calorie restriction, and the degree of anaemia appears to be related to the extent of the starvation. The anaemia . . . is not of the iron-deficiency type'. The picture presented by these Bantu thus stands in marked contrast to that observed in other people in a like condition of severe undernutrition and malnutrition. Thus during the last war, in European[21, 24], and also Japanese,[25] groups of subjects it was reported that very low haemoglobin levels occurred, although there was deposition of haemosiderin in liver, spleen, and other organs; the explanation given is that the iron pigment deposited indicated the excess of the element (derived from haemolysis) over requirement. Sherlock and Walsh,[24] noting this phenomenon in undernourished German subjects in the M.R.C. Wuppertal investigation, commented, 'Since the haemoglobin in the blood stream is below normal levels, it is uncertain why the stored iron is not used in the manufacture of new haemoglobin. It has been suggested that the intake of dietary protein may be too low to allow for the production of sufficient globulin, but there is no concrete proof of this'. Evidently, low protein intake was not a limiting factor in the case of the Bantu patients described.

Clinically healthy Bantu men and women. An endeavour was made to obtain blood from hospital orderlies and male nurses to compare with the sick men group, but this was found to be impossible on account of the reluctance of the former to give blood. As with the Shangaans examined before and after consuming a good diet, it will be noted that the mean value for the Bantu nurses after at least a year of hospital diet was not significantly different from that found upon entering hospital. The value of this observation, however, is limited by the fact that the nurses examined

on starting at the hospital were not all acclimatized to Johannesburg altitude. Hence the 2 groups of figures on the nurses are not strictly comparable.

Implications of the above observations

Knowing the uncertainties latent, not so much in haemoglobin determination, but in the difficulty of obtaining comparable groups of subjects and samples, etc., we do not desire to lay undue stress on the preciseness of our values. But our results show clearly that average values for the different groups are satisfactory or not unduly low, in spite of (1) consumption of a diet which in many respects does not contain the allowances of nutrients usually recommended, (2) occasionally gross malnutrition and undernutrition, and (3) often intense infestation by parasites, particularly hookworm.

It is apparent that a high iron intake does not necessarily promote elevated mean haemoglobin levels in groups of medically fit subjects. Such an intake, however, obviously acts as a 'brake' on the reduction of levels which would be expected under certain of the dietetic and parasitic conditions described. Briefly then, excluding a few very low values of obvious pathological origin found among the hospitalized men and women, it is maintained that for purposes of helping to assess nutritional state, no reliance should be placed on haemoglobin values in *persons habituated to a high iron intake.* This conclusion, however, also appears to be valid for persons receiving short-term iron medication.

Iron administration to iron deficient subjects. In Indian and Brazilian groups with hypochromic anaemia due to hookworm infestation, it has been shown that haemoglobin levels can be largely restored to within normal limits by iron therapy alone, without either improvement in the diet, or removing the parasites from the intestinal tract.[26, 27] In poorly nourished Chinese blood donors, hypochromic anaemia has likewise been prevented by iron therapy only, without improving the diet consumed.[28] Obviously under such conditions, an elevated haemoglobin concentration does not imply a corresponding improvement in nutritional state. A further example is afforded by the usual fall in haemoglobin concentration occurring in early infancy, which can be prevented by iron medication.[29] The observations made on this subject presumably form the basis for the recommended allowance of iron during the first year of life to be several times higher than that contained in either breast milk or the usual cow's milk mixtures.[30, 31] When marked anaemia is present the value of such therapy is undisputed. However, when breast milk is adequate in quantity there is no published evidence demonstrating that the elevated haemoglobin levels following iron administration are accompanied by improvement in nutritional state.

Iron administration to non-anaemic subjects. In non-anaemic subjects whose haemoglobin levels lie within normal limits, a high iron intake can

stimulate increased haemoglobin production. This elevation, not invariably observed, is found to be usually transient.[26, 28, 32, 33] In a particular group of subjects, namely non-anaemic white pregnant women, it has been found that, as with the Bantu pregnant women cited,[14] a high iron intake stimulates haemoglobin formation, thereby maintaining normal values throughout pregnancy,[34, 35] in contrast to the fall normally observed as pregnancy progresses.[18] In none of these instances can it be said that the rise in haemoglobin concentration was paralleled by a like improvement in nutritional state.

Finally, attention is drawn to the point that, whether it be groups of parasitized Indians or Brazilians,[26, 27] or malnourished Chinese,[28] or our local Bantu, satisfactory blood production is readily feasible on an often inadequate diet *provided it be high in iron.* For this to occur it must be inferred that the other haemopoietic factors, the extrinsic factor, vitamins B_{12} and C, etc.,[18] are supplied in sufficient amounts; alternatively, their importance in haemopoiesis must be overestimated. That the latter is probably the case is suggested by our observations on the severely malnourished hospitalized pellagrins. With their abnormal iron reserves a high level of haemoglobin concentration was maintained in spite of severe deficiencies of calories, protein and, of course, several other essential nutrients. This phenomenon, as previously noted, stands in marked contrast to experience elsewhere, where, as Hallgren[36] has recently shown from a review of the literature, protein deficiency *inter alia* is particularly liable to promote a macrocytic, or an iron-deficiency, anaemia.

SUMMARY

The diet of the South African Bantu is excessively rich in iron, mainly of adventitious origin. Various investigations have shown that in spite of an inadequate diet, sometimes gross malnutrition, and frequent parasitization, mean haemoglobin values of different groups of men and women lie within or very little below normal limits. Mean values in medically fit groups, compared with corresponding White population groups, are not invariably elevated, but observations show that the habitually high iron intake acts as a 'brake' on the depression of values that is associated with adverse dietetic and parasitic conditions. Among these people, therefore, no reliance should be placed on haemoglobin values in the appraisal of nutritional status.

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THE EFFECT OF HABITUALLY HIGH IRON INTAKE ON CERTAIN BLOOD VALUES IN PREGNANT BANTU WOMEN

BY TH. GERRITSEN AND A. R. P. WALKER

(From the Human Biochemistry Unit, South African Institute for Medical Research, Johannesburg, and South African Council for Scientific and Industrial Research, Johannesburg, South Africa)

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The influence of pregnancy on certain blood values (hemoglobin, hematocrit, serum iron, and total iron binding capacity) and their significance in the "anemia of pregnancy" have been widely investigated.

Combined evidence indicates that as pregnancy proceeds, a significant fall occurs in levels of hemoglobin and hematocrit, the explanation being that the increase in plasma volume exceeds the total increases in hemoglobin and red cells (1). In addition, evidence shows a significant rise to occur in total iron-binding capacity (2–4). There is not the same unanimity, however, with serum iron findings. Laurell (2), Lundström (5) in Sweden, and Ventura and Klopper (4) in England, have reported a fall in this value, detectable at mid-term. Yet, in America, neither Fay, Cartwright, and Wintrobe (6) nor Rath *et al.* (3) found a significant change in serum iron during pregnancy; the latter authors, therefore, alleged that the Swedish data indicated widespread iron deficiency in that country. Presumably, the same inference applies to the English series.

In South Africa, we have been greatly interested in the iron metabolism of the Bantu because: (*a*) their iron intake is often unusually high, sometimes as much as 200 mg. per diem, derived not only from the element present in their customary diet, but from adventitious iron taken up from iron utensils during the preparation of food (7); (*b*) abnormally high serum iron values are occasionally encountered in adults (8); this investigation we have confirmed and considerably extended (9); (*c*) hypochromic anemia is extremely rare (10); (*d*) at necropsy, abnormal deposition of iron is frequently seen in the tissues of the adult Bantu (11–13). We thought, therefore, that it would be illuminating to determine the above blood values, particularly serum iron levels, in groups of pregnant and non-pregnant Bantu women whose everyday diet, although deficient in many respects according to accepted standards, is characterized by an *habitually* high iron content.

MATERIALS AND METHODS

The Bantu women, examined while attending health clinics, were partly from the Johannesburg urban area, though mainly from two rural native settlements near Pretoria. Subjects were thus dwelling 4,000 to 5,000 feet above sea level. This fact must be taken into account, bearing in mind that hemoglobin concentration increases with altitude (14). Obviously, it would have been desirable to have followed a series of subjects throughout the period of gestation. But attendance at clinics is most irregular; moreover, many pregnant women do not attend until several months after conception.

The major source of calories for these people is maize, which is taken largely in the forms of cooked and sour porridges. This cereal is also used, with "kaffircorn" (sorghum), in the making of kaffir beer. These foodstuffs are usually prepared in the ubiquitous iron kaffir pots, though occasionally in paraffin cans. Several samples of foodstuffs were obtained from patients. The iron contents were determined by the thioglycollic acid method (15). Results are given in Table I.

Blood samples were taken by venipuncture between 9 a.m. and 10:30 a.m., the usual precautions being taken to prevent iron contamination. Determinations of hemoglobin, serum iron, and iron binding capacity were carried out in duplicate. Hemoglobin values were determined by the oxyhemoglobin method, using a Hilger-Spekker absorptiometer (Ilford filter 602), calibrated against total iron determinations. For hematocrit, Wintrobe tubes were used, centrifuging for one hour at 3,000 r.p.m. Serum iron was determined by the thioglycollic acid method, and iron binding capacity according to the method of Rath and Finch (16). The total iron binding capacity was calculated by adding the serum iron value to the iron binding capacity.

Since Rath *et al.* (3) have shown that the main increase in iron requirement during pregnancy occurs towards the end of the second trimester, and since the Swedish (2, 5) and English (4) workers have reported a fall in serum iron at about mid-term, we divided our subjects into two groups, one from 4 to 22 weeks, and the other from 26 to 40 weeks duration. Results are given in Table II.

TABLE I

Iron content of prepared foodstuffs consumed by our subjects

	Cooked porridge	Sour porridge	Kaffir beer
No. of samples	20	18	12
Iron content : mean range	9.9 mg./Fe/100 Gm. dry wt. (4.8–19.7)	45.0 mg./Fe/100 Gm. dry wt. (6–145)	4.2 mg./Fe/100 ml. (1.1–12.0)

N.B. South African maize contains 0.2 to 18.0, average 3.4 mg. Fe per 100 Gm. dry weight (17).

DISCUSSION

Dietary surveys by Smit (18) reveal that the quantity of maize consumed daily by the urban Bantu ranges from 6 to 21 oz. (170 to 590 Gm.) per head; that of wheat is from 5 to 15 oz. (140 to 420 Gm.). Information obtained by our dietitian, Miss J. L. Seward, on visiting homes of patients, together with information given by the patients themselves, suggest that: (*a*) the consumption of maize per diem by our subjects averaged about 1 lb. (450 Gm.); (*b*) about four-fifths of the maize bought is consumed as cooked porridge and the remainder as sour porridge; and (*c*) our subjects consumed an *average* of about 100 ml. kaffir beer per diem.

Using data given in Table I, the iron contribution by 0.8 lb. (360 Gm.) cooked maize ranged from 17 to 70 mg.; that from 0.2 lb. (90 Gm.) sour porridge, 5 to 120 mg.; that contained in 100 ml. kaffir beer, from 1.1 to 12.0 mg. Hence, the total iron ingested from these sources ranged from 23 to 202 mg., the mean value being 171 mg. per diem. Of course, additional amounts of iron are supplied by other components of the diet, *e.g.*, bread, legumes, vegetables and meat. This unusually high iron intake may be compared with the allowance currently recommended for pregnant women, namely, 15 mg. iron per diem (1)—a level not always reached by such subjects in the United States or Britain (19, 20). While we do not wish to attach undue importance to our figures, it must be stressed that these people are *habituated* to an iron intake *far higher* than that of Europeans, although the diet is deficient in several respects according to accepted standards.

Table II indicates that during pregnancy there is a significant rise in total iron binding capacity, but there is *no* significant fall in hemoglobin, hematocrit, nor serum iron.

As mentioned in the introduction, during pregnancy it is usual for hemoglobin concentration and hematocrit value to fall to a variable extent. These reductions, however, may be regarded as "physiological" and not essentially as indicative of iron deficiency. Hypochromic anemia from the latter cause is considered to be present only when the reduction in hemoglobin concentration reaches a certain level, normally placed at 11 Gm. per 100 ml. (21). The constancy of hemoglobin concentration and hematocrit levels during the pregnancy of the Bantu subjects is therefore most remarkable. One possibility is that there has been no increase in

TABLE II

Blood values in non-pregnant and pregnant Bantu women (18 to 40 years)

Period of pregnancy	Hemoglobin	Hematocrit	Serum iron (γ/100 ml. serum)	Total iron-binding capacity (γ/100 ml. serum)
	Gm. %	*%*		
Non-pregnant (48)*	13.9 ± 0.9 (12.3–16.0)	42.9 ± 2.9 (38–49)	119 ± 32 (65–195)	323 ± 45 (225–445)
0–22 weeks (43)*	13.9 ± 0.9 (12.2–15.9)	41.5 ± 3.5 (34–49)	121 ± 37 (30–205)	342 ± 54 (200–475)
26–40 weeks (49)*	13.7 ± 1.1 (11.8–17.3)	41.3 ± 3.4 (34–48)	120 ± 46 (45–280)	403 ± 58 (260–525)

* Number of subjects.

blood volume. This, however, is most unlikely, in view of the mass of published observations (at least among white pregnant women) to the contrary. A second and more likely possibility is that the increase in plasma volume as pregnancy progresses, is *quantitatively* paralleled by increases in total hemoglobin and total red cells. Whether this actually occurred must remain in doubt, since it was impracticable to carry out a series of determinations of blood volumes throughout pregnancy. Regarding this constancy of hemoglobin and hematocrit values, the following observations in the literature appear to be relevant to our subjects:

a. In the presence of a high iron intake, an otherwise inadequate diet does not prevent satisfactory hemoglobin production, even when chronic or acute hemorrhage occurs. Thus, in hypochromic anemia due to hookworm infestation, hemoglobin levels can be largely restored to normal limits by iron therapy alone, without either improvement in diet or removing the parasites from the intestinal tract (22, 23). Furthermore, in poorly nourished Chinese blood donors, it has been found that hypochromic anemia can be prevented by iron therapy alone, without improving the diet consumed (24).

b. In non-anemic subjects with hemoglobin values within normal limits, a high iron intake can stimulate *increased* hemoglobin production. This elevation, not invariably observed, is usually transient (19, 21, 22, 24).

c. In non-anemic pregnant women, it has been reported that a high intake can stimulate the production of hemoglobin and red cells, thus maintaining normal values throughout pregnancy (25, 26).

Turning now to our Bantu subjects—their diet is inadequate (low in animal protein, fat, certain vitamins and mineral salts). But during pregnancy, and for years previously, their intake of iron has been very high. Their reserves of the element are thus probably unusually large. The presence of excessive reserves is verified frequently at *post mortem;* for example, in the Johannesburg area, Higginson, Gerritsen, and Walker (13) have noted that 50 per cent of adult females reveal abnormal deposition of iron in the tissues, often to a marked degree. The explanation of unchanged blood values in pregnancy would, therefore, seem to be the unusually high iron intake of our subjects.

Our finding of no significant change in serum iron value during pregnancy agrees with the observations of the American workers (3, 6) and argues against the validity of the belief of Lundström (5) that a fall, *inter alia,* of serum iron in pregnancy, is "physiologic."

The rise we observed in total iron binding capacity is in harmony with other workers' findings (2, 4, 5). As far as we are aware, no explanation has been advanced to account for the phenomenon. There are two factors which *may be* of relevance. Firstly, iron is transported apparently exclusively by a β_1 globulin component of serum protein (27). Secondly, reduction in the albumin-globulin ratio reported to occur in pregnancy (28, 29) suggests that the concentration of the particular iron binding globulin may be increased as gestation proceeds, although it forms only a small percentage of the total globulin fraction.

SUMMARY

The iron metabolism of the South African Bantu is marked by: (*a*) an habitually high iron intake; (*b*) occasionally elevated serum iron values; (*c*) extreme rarity of hypochromic anemia; and (*d*) abnormal deposition of iron in tissues of adult Bantu examined at necropsy.

Certain blood values have been determined on pregnant Bantu women, consuming a diet characterized by its very high iron content though otherwise inadequate. On comparing data in the first and second halves of the pregnancy period, it has been found that there is no significant change in values for hemoglobin, hematocrit, or serum iron. The constancy of these values would seem to be due to the unusually high iron intake of these people.

ACKNOWLEDGMENTS

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Letters to the Editor

PROTEIN REQUIREMENTS FOR HEMOPOIESIS.

Dear Sir:

In your recent issue[1] dealing with "Nutritional Aspects of Blood Formation," Professor Vilter said "so little is known concerning the protein requirements for hematopoiesis in human beings, that no full-dress discussion of the subject was considered to be profitable." The writer considers that our information on this subject for humans is perhaps not quite as inadequate as Professor Vilter indicates.

According to Whipple,[2] experimental studies on dogs indicate that hemoglobin formation takes precedence over the formation even of serum protein, that the body stores must be greatly depleted, and the intake of protein greatly deficient over a long time before delay in hemoglobin formation occurs. Obviously, Whipple had in mind changes consequent on severe and prolonged dietary privation, and not changes in blood volume, etc., arising from minor changes in body weight.

The purpose of this letter is to suggest the following: (1) as a normal accompaniment to loss in weight, hemoglobin production diminishes at an early stage of dietary restriction when body protein stores may be little depleted and when protein intake is not necessarily low; (2) in prolonged severe undernutrition, although circulating hemoglobin mass is greatly reduced, it is probable that the amount does not fall to that level where obvious clinical manifestations would be expected; (3) in severe undernutrition, protein requirements for hemopoiesis are very small in comparison with total body protein mass and protein intake obtaining; and (4) in severe undernutrition, diminished hemoglobin production is due not to deficiency of protein or other nutrients *per se*, but rather to the concomitant low tempo of metabolism prevailing.

Amplifying these points:

(1) Reduction in weight, whether in the obese or in persons of normal weight, is accompanied by a diminution in the volume of total body fluids, including plasma. Since hemoglobin *concentration* does *not* rise during loss in weight, but is maintained, at least initially, it follows that hemoglobin production must be slowed down at an early stage when neither body protein stores nor protein intake are likely to be limiting factors.

(2) In severe undernutrition such as that present in the group of Indian prisoners of war studied by Walters *et al.*,[3] circulating hemoglobin mass fell to a mean of 345 g, approximately half the normal value. Hemoglobin concentration fell to a mean of 9.8 g per 100 ml, the scatter of values being small. Now in men and women, not suffering from severe undernutrition, observations indicate that the hemoglobin concentration can fall to 6 g per 100 ml or so, with an associated circulating hemoglobin mass of probably less than 270–300 g, before such reduction is clinically obvious.[4] Moreover, in the tropics and semi-tropics, various reports indicate that hemoglobin concentrations of as little as 2 g per 100 ml with a circulating hemoglobin mass probably less toan 100 g, are not unusually rare in patients with severe ancylostomiasis; yet observers have noted with surprise the occasional lack of obvious clinical stigmata in such sufferers. One infers, therefore, from the above and from other published evidence, that in severe undernutrition, hemoglobin mass is probably maintained at a level higher than that associated with marked clinical stigmata.

(3) The daily demand of new protein for hemopoiesis in severe undernutrition may well be less than is usually believed. In the study on the Indian prisoners already mentioned,[3] upon admission, circulating hemoglobin averaged 345 g. Assuming a 1 per cent destruction daily of red cells,[2] then 3.45 g hemoglobin had to be elaborated each day. Concerning body weight and hence body protein mass, average body weight of the Indians was not reported, but that of the grossly undernourished adult male group at Belsen studied by Mollison *et al.*,[5] averaged 44 kg. Now, according to determinations by Mitchell *et al.*,[6] and Widdowson *et al.*,[7] the percentage of nitrogen in adult cadavers is approximately 2.3 per cent, and hence, very approximately, the proportion of protein matter is about 14 per cent. In severe undernutrition, as for example that observed in the Minnesota study,[8] the *percentage* of "active protoplasmic mass" per total body

weight is known to increase. However, using the lower proportion merely for purposes of argument, protein mass of the Indian war prisoners averaged about 6 kg. The protein intake of the latter in captivity was about 15–20 g per diem. Hence, in the severely undernourished Indian subjects, calculations suggest that the amount of regenerated hemoglobin required daily was only about 1/1700th, in comparison to the total mass of body protein then prevailing, not, of course, that one considers this mass of autogenous protein even as largely available for metabolic needs. The amount, moreover, was also small, about one-fifth, in comparison to daily protein intake, although the latter was of inferior biologic value. Now the globin, or the amino acids derived from hemoglobin breakdown, are reused, at least in part. It is therefore apparent that the daily demand of *new* protein for hemopoiesis under the condition described is very small. Certainly the demand is far less than in lactation, where the high quality protein elaborated is wholly nonreturnable, and where, even in severe undernutrition, the yield of milk, although reduced, may still be considerable.[9]

(4) In the gross undernutrition observed in the Indian and Belsen studies,[3,5] (a) *normal* red cells were produced, and (b) there was no therapeutic response of the anemia to liver or iron (indeed, both hepatic and splenic siderosis, was occasionally observed). Bearing these points in mind, also that the demand for new protein in hemopoiesis is very small, it would seem reasonable to consider that delay in hemoglobin production under these severe conditions is not due to protein deficiency or to other specific nutritional deficiencies *per se*, but rather to that decreased vitality of metabolism accompanying sustained and rigorously reduced total food intake. This situation, however, still allows hemoglobin production to be maintained at a level unlikely to add a serious quota of embarrassment to an already poor clinical picture. It may be noted that Whipple,[2] in his studies on dogs, found that hypoproteinemia or anemia *per se* causes no damage to the body mechanism responsible for the production of plasma protein and hemoglobin; dogs could be kept in good health for years.

It might be added that under conditions of lesser deprivation, there is clear evidence that a low protein intake (and that of low biological value) does *not* prevent satisfactory production of hemoglobin. Thus, the hematologic picture of a group of malnourished Chinese blood donors was shown to become normal at the same rate as that of Caucasian donors, provided additional iron was ingested.[10] Again, iron therapy can restore hemoglobin concentrations to within normal limits in persons suffering severely from hookworm infestation, *without* the diet being improved and *without* the ancylostomes being removed.[11] These observations argue against the validity of the popular view that mild protein deprivation may be responsible for low hemoglobin concentrations occasionally observed under such circumstances.

The foregoing strongly supports Whipple's view cited above: indeed, the writer would go further and hazard the opinion that in humans, death from starvation supervenes before hemoglobin production is critically affected.

Now it has been demonstrated frequently that iron can stimulate erythrocytosis, particularly in women, with or without hypochromic anemia, whether pregnant or non-pregnant. While the anemia of severe undernutrition is certainly not of the iron deficiency type, one wonders whether the presence of very high iron reserves *prior* to undernutrition, may perhaps act as a brake on the fall in hemoglobin production consequent to undernutrition. The South African Bantu lend themselves well for testing this speculation, the main features of their iron picture being as follows:[12]

The iron intake of the adult Bantu is unusually high, as much as 200 mg per day: such iron is largely adventitious and derived from utensils used in food preparation; the uptake of the element is particularly marked with the traditional fermented cereal foods (pH 2–3), which are consumed very frequently and in large amounts. At necropsy, abnormal deposition of iron is apparent in the tissues of more than half of the adults examined; the distribution differs distinctly from that observed in classic hemochromatosis and transfusional siderosis, and is such as might be expected from oral iron "overload." Values for serum iron and total iron binding capacity

are frequently elevated, and occasionally are higher than corresponding values in the two diseases just mentioned. Hypochromic anemia is much less common than would be expected from the nutritional and parasitic conditions prevailing. To throw light on the above speculation, hospital records were examined of 35 Bantu men and 21 women, these subjects being amongst the most severely undernourished and malnourished patients (25–40 per cent underweight) seen at Baragwanath non-European Hospital (1500 beds) during the last five-year period. Among these patients "pure" undernutrition was rare; three-quarters were suffering from pellagra. Mean hemoglobin values, standard deviations, and ranges, after correction (13.5 per cent decrease according to Fitzgerald's Law) for the altitude of Johannesburg (5700 ft), for the 35 men were 13.1 ± 1.2, range 7.0–15.2 g per 100 ml; 37 per cent of the patients had values of 14.0 g or more per 100 ml; for the 21 women, 12.1 ± 0.8, range 6.0–15.2 g. per 100 ml; 48 per cent of the patients had values of 12.0 g per 100 ml or more. Unfortunately, clinical information was inadequate; moreover, the hematologic, biochemical, etc. data available were not determined under research conditions. Nevertheless, it is obvious that some subjects, although grossly undernourished, had unexpectedly high hemoglobin concentrations, certainly higher than values reported in corresponding studies undertaken elsewhere. What one would have wished to have known concerning these people was the precise stressful load obtaining, e.g., liver disease, pellagra, tuberculosis, syphilis, bacterial and parasitic infections, and so forth, as well as values for serum iron, blood volume, etc. In other words, one considers it very desirable to know the *maximum* stressful load, including severe undernutrition, which will still permit the maintenance of hemoglobin concentration within normal limits. The necessary investigational work to acquire such information has been planned, but it will take a considerable time before a satisfactory series of severely undernourished subjects becomes available for study.

The information given in this letter (a) underlines the extraordinary high priority given by the body, even when almost *in extremis*, to hemoglobin production: and (b) suggests that the amounts of the factors required for hemopoiesis may well be smaller than are usually believed, because they must have been contained (at least, the non-storable components) in sufficient amounts in the Bantu patients' meager diet which had been consumed in most cases for several months previously.

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—ALEXANDER R. P. WALKER, PH.D.
Human Biochemistry Research Unit, South African Council for Scientific and Industrial Research, and South African Institute for Medical Research, Johannesburg, South Africa

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tion in this organ was approximately 0.1 per cent dry weight, hemosiderin could be demonstrated by histologic methods. According to the amount of iron pigment demonstrated histologically, an attempt was made to grade the liver into one of four categories (Text-figs. 1 and 2). These corresponded approximately to the following concentrations of iron: $0 = < 0.1$ per cent; $+ = 0.1$ to 0.5 per cent; $++ = 0.5$ to 1.5 per cent; $+++ = > 1.5$ per cent. It is clear that this grading cannot

TABLE I

Cause of Death as Established at Necropsy

Primary cause of death	Male*	Female*	Total*
Cardiovascular disease	57(5)	49(6)	106(11)
Tuberculosis	22(3)	12(1)	34(4)
Neoplasia (excluding liver)	16(1)	7	23(1)
Malignant hepatic tumors	6(3)	3(2)	9(5)
Central nervous system disease	20(3)	12	32(3)
Respiratory disease	24(2)	7	31(2)
Acute bacterial infection	10(3)	8	18(3)
Genitourinary disease	8	5(1)	13(1)
Postoperative shock	1	8	9
Diabetes mellitus	0	3	3
Cirrhosis of the liver	3	1	4
Pellagra	1	0	1
Miscellaneous diseases	10(1)	3	13(1)
Total	178	118	296

* The number of cases with cirrhosis unrelated to the cause of death is shown in brackets.

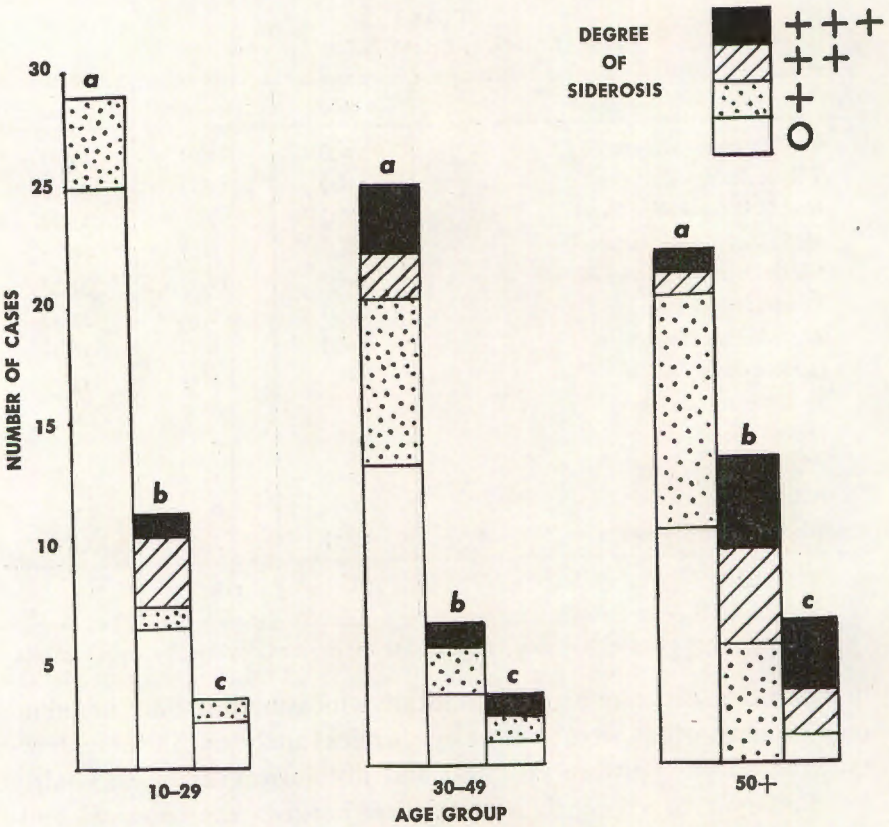
be altogether accurate as the quantitative measurements are based on only 21 cases which were studied by chemical analyses. In these, however, agreement between chemical and histologic grading was fairly satisfactory. An appropriate correlation between the chemical findings and histologic appearance was found also in other organs.

In addition the livers were classified histologically according to the degree of portal fibrosis as follows: (a) Essentially normal histology, including cases with slightly prominent portal tracts and minimal cellular infiltration. (b) Mild and moderate portal fibrosis, *i.e.*, livers with an increase in portal fibrous tissue, but without generalized confluence of the portal tracts (Fig. 2). (c) Severe portal fibrosis, *i.e.*, livers in which bands of fibrous tissue divide the organ into lobules (Fig. 3).

In this paper the term "cirrhosis" has been confined to this latter group (c).

Clinical Findings

Cause of Death. The primary diseases causing death in the complete series of 296 necropsies are shown in Table I. The degree of hemosiderin deposition was unrelated to any specific disease, and severe siderosis appeared to be an incidental post-mortem observation, not directly related to the patient's death. One patient, however, had died from the spontaneous rupture of a heavily pigmented spleen.

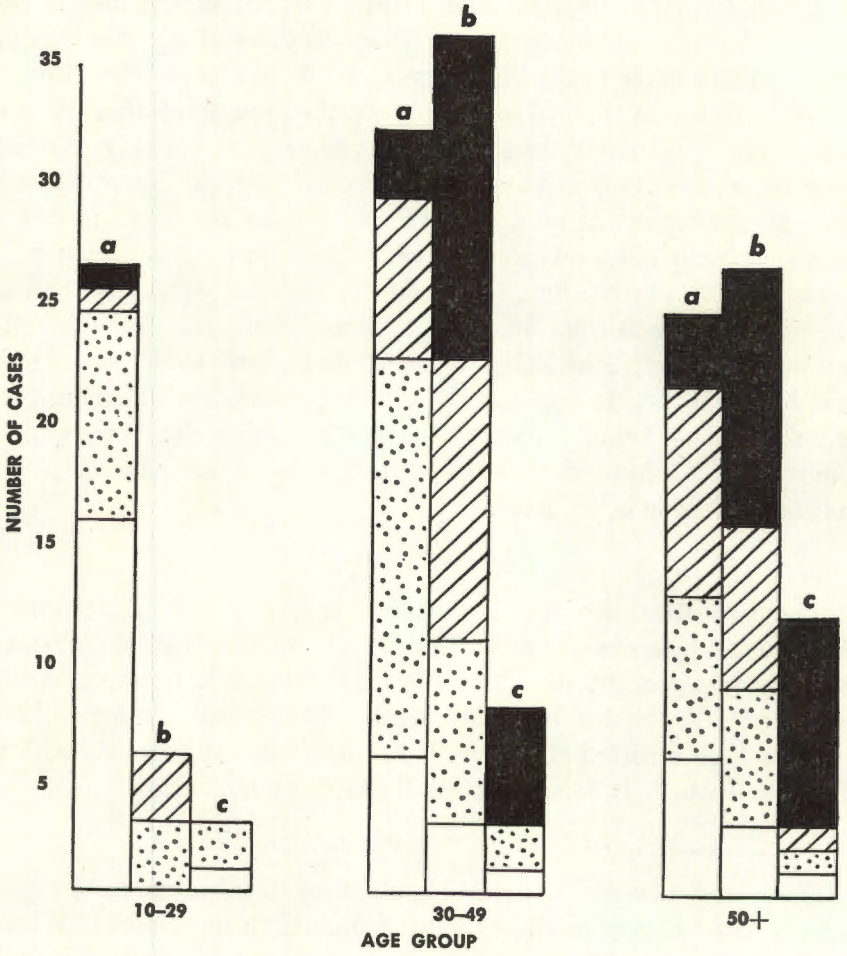


Text–fig. 1. Histogram showing the relation of hepatic fibrosis and siderosis in each age group for 118 female patients.
(a) Structurally normal livers.
(b) Livers with portal fibrosis but without confluence of the tracts.
(c) Severe fibrosis (cirrhosis).

There was no history of trauma, and except for an old focus of cerebral softening, the remaining organs and tissues were normal apart from heavy deposits of iron pigment. In 9 cases of carcinoma of the liver, a severe degree of siderosis was not found.

Nutritional State. In only 2 patients was a typical pellagroid rash observed. In the remainder the nutritional state was dependent on the

primary disease and not on the degree of iron pigmentation of the viscera. It was common, however, to find hyperpigmentation and hyperkeratosis of the skin of the limbs in Bantu patients suffering from chronic disease. Severe siderosis was seen often in wasted patients, but was observed also in the apparently well nourished.



Text-fig. 2. Histogram showing the relation of hepatic fibrosis and siderosis in each age group for 178 male patients.
(a) Structurally normal livers.
(b) Livers with portal fibrosis but without confluence of the tracts.
(c) Severe fibrosis (cirrhosis).

Diabetes Mellitus. Only 3 patients had diabetes mellitus; in these, hemosiderin deposits were very scanty.

Serum Iron. In many apparently healthy Bantu a high serum iron and total iron binding capacity have been observed.[29,30] Serum iron determinations were carried out on 5 subjects from whom liver speci-

mens were available for biopsy; of 3 patients in whom some hemosiderin deposition was demonstrable, 2 had markedly increased serum iron.

Parasitic Infestation. Schistosoma haematobium infestation was observed incidentally in 7 necropsies.

Age and Sex Distribution. The histograms (Text-figs. 1 and 2) relate the degree of siderosis to age. Under 20 years of age it is seldom observed and never to a severe degree. Its incidence and severity increase with age to the fifth decade, when the number of affected persons remains relatively constant. Females are less severely affected than males, especially in the third and fourth decades. Since it is our general experience that siderosis is very rare under the age of 10 years, younger children and infants were excluded from this investigation.

Geographic Distribution. Hemosiderin deposits were observed in the livers of Bantu from other parts of the Union, and from the following territories: Rhodesias, Bechuanaland, Swaziland, Nyasaland, and Mozambique. In many of these livers, malarial or bilharzial pigment also was found. Accordingly, the condition does not appear limited to the Johannesburg area, but as yet no extensive investigation has been made in other areas.

Chemical Analysis

The concentration of iron in the major organs from 21 Bantu and 6 European subjects is shown in Tables II to V. Cases 26 and 27 present the iron concentration in the organs of the 2 European subjects who died with classical hemochromatosis. The clinical features of case 26 have been reported elsewhere.[31] The iron concentration in classical hemochromatosis is summarized in Table V after Sheldon.[7]

Gross and Microscopic Pathologic Features

Our description of the morbid anatomical distribution of hemosiderin is based chiefly on the 44 cases examined in most detail. Where desirable, use has been made of the tissues available from the additional 252 necropsies in which the liver was examined for iron. The rusty appearance of siderotic tissues was typical, and the pattern of visceral and lymph node involvement could easily be studied with the naked eye. Further, as the pattern observed in the cases examined in more detail was constant and was confirmed by microscopy, section of further tissues was considered unnecessary.

External Appearances

The hyperpigmentation of the skin in Bantu suffering from chronic

TABLE II

Cases with a "Normal" or Low Concentration of Liver Iron (Per Cent Dry Weight)

No.	Race*	Sex	Age	Cause of death	Liver	Spleen	Heart	Pancreas	Kidney	Jejunum	Other organs		
1	E	F	60	Ruptured aorta	0.07	0.09	0.01	0.01		0.01			
2	E	M	30	Stomach carcinoma	0.06	0.13	0.04	0.03		0.01			
3	E	M	74	Pyelonephritis	0.04	0.07	0.02	0.03		0.03			
4	E	M	50	Brain abscess, cirrhosis of the liver	0.11	0.16	0.04	0.03	0.06	0.02	Thyroid gland		
5	B	F	14	Typhoid	0.08	0.25	0.03	0.04			0.04		
6	B	F	14	Mitral stenosis	0.08	0.12	0.08		0.08	0.03			
7	B	F	39	Malignant hypertension	0.11	0.11	0.03	0.04	0.08				
8	B	F	26	Obstetric shock	0.05	0.12	0.04		0.04	0.05			
9	B	F	40	Cerebral hemorrhage	0.11	0.15	0.09	0.04	0.06	0.04			
10	B	F	24	Cerebral hemorrhage	0.03	0.10	0.04	0.06	0.06	0.06			
Average European according to Sheldon[7]					0.05–0.1	0.14	0.04	0.02	0.04	0.03	Thyroid gland 0.02	Stomach 0.05	Ileum 0.03

* B = Bantu, E = European.

TABLE III

Cases with a Slight Rise in the Concentration of Liver Iron (Per Cent Dry Weight)

No.	Race*	Sex	Age	Cause of death	Liver	Spleen	Heart	Pancreas	Kidney	Jejunum
11	B	M	34	Lobar pneumonia	0.24	0.31	0.05	0.06		
12	B	M	28	Ruptured aorta	0.20	0.26	0.05	0.03		
13	B	M	45	Malignant nephrosiderosis	0.14	0.52		0.04	0.07	0.16
14	B	F	48	Nutritional heart disease	0.32	0.44	0.06	0.05		0.09

* B = Bantu.

TABLE IV

Cases with Moderate Increased Concentration of Liver Iron (Per Cent Dry Weight)

No.	Race*	Sex	Age	Cause of death	Liver	Spleen	Heart	Pancreas	Kidney	Jejunum	Other organs	
											Portal lymph node	Jejunal lymph node
15	B	M	60	Chronic nephritis	0.52	2.15	0.04	0.08		0.07		
16	B	M	30	Tuberculous meningitis	0.56	0.96	0.05	0.09	0.09	0.80		
17	B	M	63	Bronchopneumonia	0.74	2.86	0.06	0.14	0.10	0.38		
18	B	F	60	Chronic pyelonephritis	0.71	1.12				0.43		
19	B	M	42	Nutritional heart disease	1.23	2.63	0.05	0.09	0.09	2.12	5.85	3.64
20	B	M	65	Cerebral thrombosis and tuberculosilicosis	1.19	3.73	0.09	0.07	0.05	0.33		

* B = Bantu.

TABLE V

Cases with High Concentration of Liver Iron (Per Cent Dry Weight)

No.	Race*	Sex	Age	Cause of death	Liver	Spleen	Heart	Pancreas	Kidney	Jejunum	Other organs		
											Stomach	Ileum	Thyroid gland
21	B	M	45	Tuberculous meningitis	1.55	5.16	0.07	0.08	0.18	1.43	0.07	0.06	0.05
22	B	M	42	Hypertensive congestive circulatory failure	2.34	5.75	0.05		0.17	1.08			
											Stomach	Duodenum	Ileum
23	B	M	50	Generalized tuberculosis	2.45	3.50	0.07	0.15	0.10	1.41	0.09	0.42	0.23
											Stomach	Ileum	Bone marrow
24	B	M	63	Pulmonary tuberculosis	3.59	6.01	0.15	0.13	0.15	1.84	0.05	0.04	1.09
25	B	F	60	Lobar pneumonia	5.52	10.5	0.07	0.49		0.31	Stomach		
26	E	F	25	Acute cardiac failure due to hemochromatosis	2.56	0.39	0.51	0.71	0.13	0.16	0.20		
											Stomach	Ileum	
27	E	M	48	Acute heart failure due to hemochromatosis	3.25	0.25	0.37	0.79	0.3	0.10	0.24	0.08	
											Stomach	Ileum	Thyroid gland
Average concentration and range in hemochromatosis according to Sheldon[7] (1935)					3.6 (1.0–7.6)	0.6 (0.2–0.8) one case, 2.6	0.5 (0.2–1.0)	2.0 (0.06–5.0)	0.2 (0.07–0.5)	0.15 (0.6–0.02)	0.2 (0.1–0.3)	0.06 (0.06–0.07)	0.5 (0.2–1.2)

* B = Bantu, E = European.

disease was due to increased melanin in the rete malpighii and was unrelated to the amount of hemosiderin in the abdominal organs. In 3 of 10 severe cases with heavy iron pigmentation of the liver, microscopic examination of the skin from the flexor surface of the arms showed a few scattered hemosiderin granules in the corium, most marked in the region of the skin appendages. No iron pigment was found in skin sections from cases with moderate hepatic involvement.

The Liver

The following description is drawn from the 292 livers examined. The gross appearance varied according to the nature of the primary disease. In livers with a moderate or severe siderosis, the organ had also a rusty brown color and gave a positive Prussian blue reaction in the cold. In 35 of these 292 livers, cirrhosis was present but in only 4 was it the direct cause of death. The weight of the organ was unrelated to the intensity of pigmentation. The mean weight for normal livers without histologic iron was 1515 gm. (range, 1120 to 2000 gm.); for those classified as severe siderosis, 1550 gm. (range, 1200 to 2350 gm.); and for those with fine multilobular cirrhosis, 1660 gm. (range, 1200 to 2450 gm.).

Microscopic Examination. Among Bantu patients it is common at necropsy to find histologic evidence of liver disease, which is apparently unrelated to the cause of death (Table I). Similar lesions are observed in liver specimens for biopsy from patients who clinically are not under suspicion of having hepatic disease. These lesions vary from prominence and slight fibrosis of the portal tracts to a fine multilobular cirrhosis (Figs. 1 and 2). There may be an associated pleomorphic portal infiltration by lymphocytes, plasma cells, and histiocytes, also polymorphonuclear cells and eosinophils. Throughout the liver, the fibrosis of the portal tracts is unequal; in some tracts there is little or no increase in fibrous tissue; elsewhere collagen fibers extend toward the neighboring tracts and between the parenchymal cells at the periphery of the lobules. The resultant cirrhosis accordingly shows both a monolobular and multilobular distribution. It seems probable that, in the late stages, such a cirrhosis may progress to a coarse cirrhosis morphologically indistinguishable from that of post-necrotic origin, but proliferation of the bile ducts is insignificant and necrosis of the liver cells is not a feature. The distribution of the livers of the various types in each group is shown in Text-figures 1 and 2.

Of the 35 cirrhotic livers, the cirrhosis in 25 was clearly a more advanced degree of the fine portal type which we have described. In

none of these was it considered the direct cause of death. There was one case of true biliary obstructive cirrhosis. The remaining 9 livers showed a coarse multilobular cirrhosis. In the latter cases the clinical history was insufficient to determine the etiology with certainty.

Distribution of Iron Pigment. In the majority of livers, hemosiderin was observed in both liver and Kupffer cells. In cases of mild siderosis the cytoplasm of the Kupffer cells usually stained a diffuse blue and sometimes contained small hemosiderin granules. In the parenchyma, on the other hand, iron pigment appeared first as fine granules at the biliary pole of the hepatic cells at the periphery of the lobules. In 8 livers, however, hemosiderin was found only in the Kupffer cells (Fig. 3), and in 8 additional livers pigment was confined almost entirely to the parenchymal cells, pigment in the reticulo-endothelial cells being insignificant.

In severe cases, the deposits of pigment in the parenchymal cells and Kupffer cells were more marked and the pigment granules of larger size. Deposits, however, were still most obvious in the liver cells at the periphery of the lobules, but the pigment was no longer confined to the biliary pole (Figs. 4 to 6). Where the Kupffer cells were heavily involved, large granules of pigment obscured nuclear detail and the cells appeared as masses of granular hemosiderin. In an occasional case, iron-laden multinucleated macrophages were present in the sinusoids. Even where deposits were marked in the liver cells, cellular degeneration was not a prominent feature. No correlation was observed between the amount of hemosiderin in the Kupffer cells and in the liver cells.

In siderotic cases of all degrees of severity, deposits of iron pigment were noted also in the portal tracts (Figs. 5 and 6). These varied from an occasional iron-laden macrophage to heavy intracellular and extracellular masses. The appearance of these latter masses suggested origin from the disruption of iron-laden macrophages. Frequently, in cases with severe pigmentation, hemosiderin was found in the epithelium of the small bile ducts, and in the endothelial cells of the portal lymphatics and venous channels. Invasion of the liver capsule by iron-laden macrophages was always present in association with heavy pigmentation of the portal tracts. The histograms (Text-figs. 1 and 2), however, show that all patterns of liver damage can be associated with any degree of hemosiderin deposition. But while there is a tendency for severe siderosis to be associated with portal fibrosis and cirrhosis, conversely, some cases with heavy iron storage show little or no fibrosis.

In siderotic livers, foci of scarring or tuberculosis were often infil-

trated by iron-laden macrophages (Fig. 7). Similar invasion of fibrous scars was found elsewhere in the body.

Iron Content. On comparing the concentration of iron determined chemically and assessed histologically in 21 livers, it was clear that the fibrosed portal tracts permitted marked storage; *i.e.*, when a liver showed a high iron concentration on chemical analysis, much of the hemosiderin appeared to be situated in the portal tracts. In this series, the highest concentration of hepatic iron was 5.52 per cent dry weight (case 25). In this liver, cirrhosis was present.

Spleen

In siderotic cases the spleen showed a marked rusty color, the intensity of which was invariably greater than that in the liver. Sometimes, although the liver had a normal color, the spleen showed a distinct brownish tinge and gave a positive Prussian blue reaction. The weight and size of the organ were related to the accompanying disease process. Significant enlargement of the spleen or other evidence of portal hypertension was present in only 6 of the 25 cases with fine multilobular cirrhosis.

On microscopic examination of the 113 spleens available, a much greater concentration of iron was found than in the liver, with only 2 exceptions. This was confirmed by chemical analysis in 21 cases (Tables II to V) but the total quantity of iron, however, was less than in the liver. In those cases in which only minimal involvement of the parenchymal or Kupffer cells of the liver was present, the spleen showed significant deposits of hemosiderin in the endothelial cells and macrophages. In more severe cases, the number of iron-laden macrophages in the pulp increased to form dense masses, some of which appeared extracellular (Fig. 8), and often the entire reticulo-endothelial system was outlined by pigment. Iron-laden histiocytes were found also in the capsule and trabeculae, and the endothelium of the trabecular veins frequently contained hemosiderin granules. Occasionally, slight iron encrustation of the trabecular fibers was observed, but the elastica of the vessels was usually unaffected. The malpighian corpuscles appeared relatively free from iron pigmentation. Fibrosis was not significant unless some other factor such as portal hypertension or chronic venous congestion was present.

Pancreas

On naked-eye examination the pancreas usually appeared normal, but in 2 cases it had a distinct brown color. Of the 82 pancreases ex-

amined microscopically, 32 were from cases in which the liver was heavily pigmented. In the majority of these, slight hemosiderin deposits were noticed in scattered interstitial macrophages, but in only 7 did the acinar and islet cells contain iron-pigment granules. These were very scanty with the exception of case 25, the most severely siderotic case noted. Cases of moderate or mild hemosiderosis showed no evidence of epithelial involvement. Chemical determination confirmed the very low concentration of iron in the pancreas, in contrast to that in the liver and spleen. In a few cases there was a fine interstitial fibrosis which was unrelated to the amount of iron in the pancreas or in other viscera.

Heart

In only 4 of the 21 hearts from cases with severe hepatic siderosis were iron pigment granules observed in the perinuclear region of the myocardial fibers. In the remaining 53 hearts from cases of lesser severity, no iron could be demonstrated histologically in the myocardium. Chemical analysis confirmed the very slight increase in iron in the cardiac muscle.

Kidney

In both severe and moderate cases, scanty hemosiderin granules usually were found in the distal convoluted tubules and also in the loops of Henle. In some severe cases granules of iron pigment were found lying in the glomerular capillaries. Scattered hemosiderin-laden macrophages frequently were present in the interstitial tissues as were also slight extracellular deposits, especially in foci of fibrosis. The tubular deposits were scanty and focal in distribution. Analysis in 4 severe cases showed only a slight increase in iron concentration.

The Gastrointestinal Tract

The stomach appeared normal, even in patients with severe siderosis on gross examination. In 4 very severe cases, microscopic examination showed only traces of hemosiderin in a few acinar cells and only occasional iron-laden macrophages in the submucosa. In 6 other cases with equally heavy visceral deposits, no pigment was found in the epithelial cells.

On naked-eye examination the duodenal and jejunal mucosa from cases with slight hepatic pigmentation appeared normal. In cases with more marked visceral involvement, however, the mucosa had a rusty color and gave a positive Prussian blue reaction. This color was first noted in the doudenum (being most intense in the third and fourth parts) and upper jejunum, and then diminished and disappeared in

the lower jejunum and ileum. Microscopic examination confirmed the gross appearances in mild cases; sections of the jejunum showed only an occasional iron-laden macrophage in the substantia propia of the villi. But in severely siderotic cases all cellular detail in the villi was obscured by masses of intracellular and extracellular pigment. Similar changes were found to a lesser degree in the duodenum, but in no case examined were the glands of Brunner involved (Figs. 9 and 10). When the visceral deposits of hemosiderin were slight, the ileum showed no abnormal storage, but in severe cases a few iron-laden macrophages were found in the villi. The colon was normal, but occasionally, foci of hemosiderin-laden macrophages were found in the mucosa. In all cases post-mortem change was too advanced for examination of the epithelium.

Chemical analysis confirmed the histologic findings; the iron concentration of the stomach, ileum, and colon showed insignificant rises in comparison to the jejunum, which on one occasion contained seventy times the average normal value (case 21). Due to the presence of the muscle in these specimens, however, these values are only approximate and the actual mucosal concentration of iron would be much greater. From Tables II to V, it can be seen that a rise in the concentration of iron in the jejunum usually accompanied an increase in the liver and spleen, and this was confirmed by histologic study.

Slight deposits of hemosiderin were found in the acinar cells of only 2 of 12 *parotid glands* examined. No hemosiderin or only an occasional iron-laden interstitial macrophage was observed in 4 additional glands, although all 6 subjects showed equally heavy iron deposits in the abdominal organs.

Endocrine Glands

Sections from the thyroid gland, pituitary body, and testes showed only a few scattered hemosiderin-laden macrophages in the interstitial tissues. In only two thyroid glands from severe cases were hemosiderin granules found in the epithelial cells. Of the 19 suprarenal glands examined, in only 2 was iron pigment found in the epithelial cells. In many of the remainder, although the endothelial cells of the cortical sinuses were outlined by hemosiderin and heavy deposits were present in the medulla, no pigment was observed in the epithelial cells.

Testicular atrophy and gynecomastia were present in several cases, but no correlation with the degree of visceral siderosis or hepatic cirrhosis could be established.

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SIDEROSIS IN THE BANTU OF SOUTHERN AFRICA *

J. HIGGINSON, M.B., TH. GERRITSEN, D.Phil., and A. R. P. WALKER, Ph.D.
(From Baragwanath Non-European Hospital; and the Human Biochemistry Unit, South African Council for Scientific and Industrial Research. South African Institute for Medical Research, Johannesburg, South Africa)

Extensive deposition of hemosiderin in the viscera of the South African Bantu was first described by Strachan,[1] and later by the Gillmans and their co-workers.[2-5] Strachan considered metallic poisoning by copper, tin, or zinc the probable etiologic factor. Gillman and Gillman[3] correlated the abnormal iron deposits with pellagra and malnutrition.

The general physiology and pathology of iron storage has been reviewed recently by Finch and his associates.[6] In man, large hemosiderin deposits are found mainly in classical or idiopathic hemochromatosis,[7] in certain anemias,[6,8,9] and after multiple blood transfusions.[10-12] In undernutrition or starvation, iron pigment deposits are found also, probably due to the breakdown of blood and tissue cells.[13,14] Heavy visceral deposits of iron, associated with bone and joint deformities, have been reported also in Korean mountain dwellers.[15]

In animals, the parenteral administration of citrated blood or iron compounds leads to excessive amounts of iron in various organs; this has been observed in mice,[16] rats,[6] rabbits,[17-20] and dogs.[6,21] The addition of iron salts to certain experimental diets, especially if low in phosphorus, also has been shown to cause excessive iron deposition in various animals.[6,22-24]

The pattern of iron distribution in severe siderosis in the Bantu has been assumed to be identical to that in classical hemochromatosis;[1-5,25,26] but our findings, which are the result of anatomical, histopathologic, and chemical investigation, do not support this view and accordingly seem worthy of publication.

METHODS AND MATERIALS

Our investigation was based mainly on 44 necropsies representing siderotic cases of varying severity. The liver, spleen, heart, kidney, and pancreas were examined in each, with the exception of the kidney in one case. Blocks from the jejunum also were available in 32 of these necropsies. In selected cases, additional blocks were taken as

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desired from the gastrointestinal tract, salivary glands, endocrine glands, lymph nodes, bone marrow, breast, tongue muscle, and skin.

In 21 of these cases, the iron concentration was determined in selected organs. With two exceptions this had to be done on formalin-fixed tissues and no allowance could be made for hemoglobin iron. However, since the quantity of iron as hemosiderin was so large, the small amount of hemoglobin iron would not have been significant, as was shown by Roth, Jasiński, and Bidder.[27] The tissues were dried at 110° C. for 24 hours, ashed at 450° C., and the iron estimated by the thioglycollic acid method. In the majority of organs the iron concentration was determined in duplicate. The duplicates showed a maximum error of about 10 per cent. In addition, tissues of 4 European adult subjects were analyzed as controls. The iron concentration also was determined in the major organs of 2 cases of classical hemochromatosis in Europeans.

To establish the incidence of siderosis and its relationship to hepatic fibrosis, 252 additional necropsies were reviewed, and the livers sectioned and stained for iron. The pattern of iron distribution was confirmed in these necropsies by the study of a small number of random tissues.

Both the more detailed series of 44 necropsies and the additional 252 cases were unselected, except that children under 10 years, and patients with anemia, malaria, and hepatic necrosis were omitted.

Also examined were 110 specimens of liver obtained for biopsy from other patients, many of whom showed various stigmata of malnutrition. Additional blocks from 72 livers obtained from unselected necropsies of Bantu living in other territories in Southern Africa also were available for examination.

In general, the organs were fixed in 10 per cent formalin; but in a few cases formol-sublimate, or Carnoy's fluids, were used. All sections were stained routinely with hematoxylin and eosin. Hemosiderin was demonstrated by Perls' hot potassium ferrocyanide method, modified after Dry.[28] The sections were counterstained with basic fuchsin. Additional stains used in selected cases were Turnbull's blue, Sudan IV, Sudan black, Mallory's picric acid-stain after McFarlane, silver reticulin stain, and Schiff's periodic acid stain with or without preceding salivary digestion.

Classification of Cases

Since the liver stores a high proportion of the total body iron, the concentration of the element in this organ was used arbitrarily as a standard of severity for each case. Usually, when the iron concentra-

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Iron Intake and Hæmochromatosis in the Bantu

THE high incidence of hæmochromatosis among the Bantu was initially pointed out by Strachan[1], and has been confirmed by the Gillmans[2,3], who regard the disorder as one of the manifestations of chronic malnutrition.

In a recently published paper, Kinney, Hegsted and Finch[4] have reported, *inter alia*, that : (*a*) when rats were fed on an adequate diet together with 2 per cent iron citrate, no deposition of hæmosiderin occurred in the liver ; (*b*) when a diet of 80 per cent corn grits and 20 per cent lard was used, there was slight deposition of hæmosiderin in that organ ; (*c*) but when this latter diet was supplemented with 2 per cent iron citrate, massive deposition resulted. Only, therefore, when the diet was inadequate in many respects and also contained added iron was the accumulation of this element in the liver observed. The general pattern of the distribution of iron in the tissues of the rats was stated to be similar to that observed in the Bantu subjects. Since the diet of the Bantu usually contains a large amount of maize, the above considerations have prompted inquiry as to the level of the daily iron intake of these people. The purpose of this communication is to provide evidence that an unusually large amount of iron is, in fact, frequently ingested in their food.

It has been stated that the diet of the African is not particularly rich in iron[5] ; but a daily diet including maize to provide, say, 2,000 calories contains 15–30 mgm. iron, thus probably more than covering the generally recommended allowance of 10–15 mgm.[5]. The intake of this element, however, is greatly increased during the preparation of food for consumption, for the Bantu, both in rural and urban areas, very frequently use iron pots for cooking purposes. It has been found that in the cooking of whole maize, maize meal porridge, various types of legumes, and in the preparation of kaffir beer and fermented porridge or 'marewa', the iron content may be increased up to at least five times that contained in the original foodstuffs. A typical diet cooked in the traditional manner may contain 100–150 mgm. iron per diem. When large numbers of Bantu are fed in a communal manner, large iron cooking vessels are also used. Analyses for iron content of the adequate diets consumed have been

undertaken at certain centres : the daily food ration of the Bantu workers on the gold mines and at this Institute has given values of 100–150 mgm. iron per diem ; while values of about 100 mgm. per diem have been obtained in the food intake of Bantu prisoners at the Johannesburg Gaol.

Confirmation of the large amounts of iron being ingested by these people has been obtained by determining the iron content of their fæces. In the case of the gold mine Bantus (three-day periods) and the Institute Bantus (one-day periods), the amounts of iron voided varied from 75 to 145 mgm. per diem ; for the gaol Bantus (seven-day periods), the amounts varied from 65 to 105 mgm. per diem. Far less accurate but confirmatory evidence has been obtained by determining, with suitable precautions, the iron content of stools of rural Bantu collected at kraals in the countryside near Johannesburg ; values from 40 to 215 mgm. per stool were obtained. Urines, collected for 24-hour periods, from subjects at the above centres, all contained less than 0·7 mgm. iron per diem. Balance experiments for weekly periods have been carried out on the Bantu prisoners at the gaol, when consuming their everyday food ; since, however, the homogenization of food before consumption was not carried out, the iron-intake figures, and hence the iron-retention figures, are not reliable.

It is obvious from experiments both on animals and man that a high intake of iron is not the cause of hæmochromatosis. Nevertheless, the study of Kinney *et al.*[4] showed that, in the unsatisfactory dietary setting used, such an intake was of critical importance in promoting the development of the disorder. It is therefore suggested that with the particular type of malnutrition affecting the Bantu, the relatively large amount of iron habitually ingested may be an etiological factor in the hæmochromatosis reported to be so common among them.

A. R. P. Walker
U. B. Arvidsson

Nutrition Unit,
Council for Scientific and Industrial Research,
South African Institute for Medical Research,
Johannesburg. April 3.

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ABSORPTION OF IRON

[*To the* EDITOR *of the* BRITISH MEDICAL JOURNAL]

SIR,—I read with interest your leading article on the absorption of iron (February 3, p. 231), because abnormal deposition of the element is frequently observed in the South African Bantu living on the Witwatersrand (investigations up to the present have been limited to these people).[1,2]

Haemosiderosis—apart from being a feature of haemochromatosis—can arise from a high oral intake of iron, from its intravenous administration, from diseases marked by haemolysis, and possibly from malnutrition. Since it has been found that the iron intake of these Bantu is frequently as much as 200 mg. per day, derived mainly from their iron cooking vessels,[3] the role of this high intake, as a causative factor in the haemosiderosis observed, seems worth considering. An interesting observation, barely mentioned in current reviews on iron metabolism, is that, when iron preparations are taken orally in doses of the order used in iron therapy, an abnormal amount, sometimes reaching several grammes, is absorbed by the body. Such iron is retained and not excreted. This abnormal absorption has been observed to occur not only in anaemic persons[4,5] but also in normal or non-anaemic subjects.[5,6] It seems, therefore, that the usual response to a high intake of iron is an excessive retention; in other words, under such conditions of intake the "mucosal block"[7] ceases to operate effectively.

Returning to the local Bantu—the iron provided by their cereals, legumes, etc., is already relatively high—say, up to 40 mg. per day. When these foods are cooked in iron vessels—the ubiquitous kaffir pots and paraffin cans, also the larger iron containers used in communal feeding—this intake may be doubled. When, however, fermented maize porridge (*marewa*) and kaffir beer, of *p*H values about 3.5, are prepared, the uptake of iron may reach ten times the amount contained in the parent cereals. It must be emphasized that such food preparations are national and traditional to these people, and are frequently consumed in large amounts by men, women, and even children. Analysis of the total diets consumed and also of stools from widely different sources gives the impression that a high intake of iron, sometimes exceeding 200 mg. per day, is of common occurrence. Balance observations[4,8] have shown that an intake of this order lies within the range wherein excessive

retentions are likely to occur. Can these intermittent though cumulative retentions be responsible for the haemosiderosis ?

Of the other possible causes, malaria is the only common disease marked by haemolysis which, if chronic, could give rise to intense haemosiderosis. But Gillman and co-workers have pointed out that, since typical malarial livers were found so seldom in the haemosiderotic cadavers studied by them, malaria cannot be responsible for the frequently observed haemosiderosis.[8] As a causative factor, blood transfusions obviously can be neglected.

As to malnutrition, American workers have shown, with animals, that an abnormal absorption of iron may be caused by certain types of inadequate diet—for example (*a*) when composed of 80% maize or rice and 20% lard,[9] or (*b*) when deficient in pyridoxin.[10] Such haemosiderosis is increased by the presence of a high iron intake. Turning to man, one might remark that malnutrition is not new, nor is it confined to backward pigmented peoples ; moreover, the phenomenon of haemosiderosis was well known towards the end of the last century. In Europe at that period poverty was not uncommon. If, therefore, malnutrition *per se* is a causative factor it is difficult to understand why able German pathologists like Quincke, who were keenly interested in the subject, failed to report a type of haemosiderosis peculiar to poorly nourished people. It could be argued that the undernourishment then occurring was too mild to provoke the phenomenon, or that the latter was of too infrequent occurrence to attract special attention. Yet our Bantu are not the most malnourished of peoples.

Surely if malnutrition is causative, haemosiderosis should be proportionately common among less-favoured inhabitants of the East. So far as I can determine there is no evidence that this is the case. Absence of reports does not, of course, establish that intense haemosiderosis does not occur, but their lack gives the impression that malnutrition *per se* is not the critical factor. On the other hand, it is conceivable that a particular type of malnutrition is involved. The point you noted, Sir, in relation to a low phosphate diet promoting the absorption of iron does not seem to have a bearing on the haemosiderosis in the Bantu, for the nature of their diet is such that their intake of phosphorus is unusually high.

There would seem to be at least three possible hypotheses on the causation of this " dietary haemochromatosis " maintained by Gillman and co-workers to be one of the manifestations of chronic malnutrition.[8]

(1) Under certain conditions the consumption of an inadequate diet gives rise to a malnutritional picture which includes, *inter alia*, kwashiorkor, pellagra, hepatic cirrhosis, primary carcinoma of the liver, and also haemosiderosis.

(2) Under certain conditions the consumption of an inadequate diet causes a lesion which, as in (1), allows abnormal absorption

of iron to occur; but the amount absorbed reaches significant proportions—i.e., the haemosiderosis becomes prominent—only in the presence of a high intake of iron, the latter being common and apparently peculiar to the Bantu.

(3) The haemosiderosis is caused primarily by the high iron intake (there is no necessity to postulate a lesion of the digestive tract), in which case the diseases occurring simultaneously are fortuitous superimpositions.

A certain amount of evidence from both animals and man may be cited in support of each hypothesis, but present knowledge is insufficient to establish the probable explanation. It is necessary to know more of the character of the haemosiderosis—i.e., of its extent, distribution, and histological picture in the organs and tissues affected—and of how the incidence is influenced by malnutrition generally, by the type of cereal consumed (maize, kaffir corn, etc.), by the amount of acid-fermented foodstuffs consumed, and so forth. It is, alas, all too easy to theorize. One would be grateful for any comments your readers may care to make on this phenomenon which occurs so frequently among these people.

This letter is published with the permission of the South African Council for Scientific and Industrial Research.

—I am, etc.,

Pretoria.

ALEXANDER R. P. WALKER,
Senior Research Officer, Nutrition Unit,
National Chemical Research Laboratory,
South African Council for Scientific and
Industrial Research.

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Iron "Overload" in the South African Bantu

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A. R. P. WALKER, M.SC., PH.D.

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ULLA B. ARVIDSSON, B.SC.

Human Biochemistry Unit, South African Institute for Medical Research, and South African Council for Scientific and Industrial Research.

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At the Johannesburg Gaol, balance experiments have been carried out on a number of Bantu prisoners when consuming their usual high cereal diet. Among various observations made, it was puzzling to find that the chemically determined value for iron intake was almost invariably higher than the value calculated from good tables. Subsequent investigation revealed the difference in values to be mainly due to adventitious iron taken up from iron vessels during the preparation of their food. Since the vessels in question are used frequently in communal feeding, and since iron kaffir pots and, to a lesser extent paraffin cans, are ubiquitous in rural areas and urban townships, it was considered that the level of iron intake of the Bantu might well be higher than is usually supposed.

In South Africa, it has been found that siderosis or abnormal deposition of iron is frequently present in organs and tissues of adult Bantu examined at necropsy (STRACHAN, 1929; GILLMAN et al., 1945a; HIGGINSON et al., 1953). It was therefore thought worth while to investigate the range of iron intake among various population groups. In the light of such knowledge, it should be possible to discuss the likely physiological or pathological effects of a habitually high iron intake, and so learn whether this could be responsible for the widespread siderosis observed.

The uptake of iron from such utensils during food preparation has been reported by other workers (MCCANCE and WIDDOWSON, 1943; MACKAY et al., 1947). But whereas the uptake in the everyday preparation of food by Western peoples is not likely to be of much practical nutritional importance, the position with the Bantu is different. First, their diet includes a variable though usually large amount of cereals, providing initially a relatively large contribution of the element. Second, the preparation of extensive amounts of staple foods in iron utensils clearly makes for a high potential contribution of extraneous iron. Particularly is this likely to be the case with acid fermented foodstuffs, e.g., porridge (*marewa*) and kaffir beer (pH 3.0-3.5), large volumes of which are consumed, sometimes daily. We have therefore determined :

(1) The uptake of iron from iron kaffir pots and paraffin cans during the cooking of whole maize, maize meal porridge, and common legumes, using Bantu methods of cooking.

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(2) The iron content of Bantu foodstuffs prepared for consumption, such being obtained from a wide variety of sources; and

(3) The iron content of samples of Bantu stools and urines.

MATERIALS AND METHODS

Iron uptake in foodstuffs cooked in the laboratory. The iron kaffir pot (capacity 7 pt.; weight 8 lb.) and paraffin can (capacity 4 gal.) employed were similar to those commonly used by the Bantu. Whole maize, maize meal (household), " cow peas " (*Vigna unguiculata*), and " sugar beans " (*Phaseolus vulgaris*), were added to different proportions of tap water and cooked for varying periods in pot and can. Our dilutions and times of cooking were those in popular use. The tap water contained 0.5 mg. iron per l., a negligible contribution. In South Africa the iron content of various surface and underground waters examined by the Railways and Harbours Administration ranges from 0.02-2.5 mg. iron per l.; the amount afforded by a daily consumption of, say, 2-3 l. is small, so that the average contribution from potable water need not be taken into account. The iron contents of the uncooked compared with cooked foodstuffs examined are given in Table I.

TABLE I. Laboratory experiments on uptake of iron in cooking of Bantu foodstuffs in iron kaffir pots and paraffin cans.

(All results expressed as mg. iron per 100 g. dry substance unless otherwise stated).

Foodstuff	No. Detns.	Before cooking		After cooking			
				In pot		In can	
		Range	Average	Range	Average	Range	Average
Maize on cob	6	2.9-4.1	3.6	3.5-4.8	4.2	3.3-4.6	4.0
Maize meal porridge (household)	6	3.9-4.5	4.3	4.7-9.2	7.9	4.5-8.1	6.8
" Cow peas "	6	5.5-8.0	7.6	19.4-41.6	29.9	12.5-33.1	19.4
" Sugar beans "	6	5.9-7.1	6.6	11.1-19.9	16.7	9.6-21.8	13.6

TABLE II. Iron content of foodstuffs prepared for or by Bantu.

Foodstuff	Gaols	Hospitals	Mine compounds	This Institute	Urban sources	Rural sources	Average
Whole maize	8.8 (5)*	—	—	6.9 (4)	8.1 (4)	6.9 (3)	7.5
Maize meal porridge	8.2 (11)	15.0 (6)	9.1 (8)	7.1 (5)	7.9 (6)	9.2 (7)	9.7
Maize meal sour porridge (per 100 ml.)	—	2.0 (5)	2.1 (10)	3.4 (15)	2.7 (10)	2.9 (9)	2.4
Kaffir beer (per 100 ml.)	—	—	3.8 (6)	—	4.8 (5)	6.1 (5)	4.7
Legumes	17.0 (9)	—	12.2 (3)	11.1 (5)	11.9 (8)	12.9 (5)	12.3

* ( ) denotes number of samples.

Iron content of prepared foodstuffs obtained from different sources. Iron was determined on samples of maize porridge, fermented porridge (*marewa*), kaffir beer, and beans, obtained from prisons, hospitals, mine compounds, this Institute, and from homes of urban and rural

Bantu. Results are given in Table II. Estimations of total iron intakes of different groups of subjects, calculated from Table II, and from knowledge of the amounts of the different foods consumed, are given in Table III.

Iron content of Bantu stools and urines. Stools were collected from prisoners at the Gaol (7-day periods) and from mine labourers (3-day periods); their iron contents are given in Table IV. In addition, single stools were collected, with precautions against iron contamination, from the countryside within an area of 25 miles around Johannesburg. The iron content of 56 stools ranged from 10 mg. to 360 mg. Twenty-four hour samples of urine were collected from (a) three gaol Natives, (b) five mine labourers, and (c) three Natives from this Institute, all known to be habituated to a high iron intake. Iron contents ranged from 0.05 mg. to 0.7 mg.

Determination of iron. Iron in foodstuffs and stools was determined by the thioglycollic acid method; and in urines by the thiocyanate method, as described by McCANCE and SHIPP (1933) and McCANCE et al. (1936) respectively.

TABLE III. Iron content of daily diet of various Bantu groups.

Source	Number of sources	Range of intake mg./diem
Gaols	2	48-110
Hospitals	2	35- 85
Mine compounds	6	45-190
This Institute	1	40-215
Urban homes	5	35-185
Rural homes	6	30-150

TABLE IV. Iron content of stools collected for known periods.

Number of subjects		Period of observation (days)	Iron voided mg. per diem
Gaol	3	7	65-105
Mines	4	3	50-160
This Institute	2	1	75-145

DISCUSSION

The iron contents of the prepared foodstuffs obtained from different sources (Table II) confirm the results of our laboratory cooking experiments (Table I). Using data given in Table II, and knowing approximately the amounts of each foodstuff consumed, we have found the iron intake of the Bantu groups examined to range from 35 to 215 mg. per diem (Table III).

The data on the faeces collected for known periods (Table IV) confirm the validity of high iron intakes. The iron contents of the stools collected from the countryside support our view of the commonness of the high intakes.

The values for the 24-hour samples of urine are in harmony with the accepted view that the amount of iron excreted by the kidneys is negligible, even when the level of intake is several times higher than that of everyday experience (McCANCE and WIDDOWSON, 1937).

While it is apparent that the different types of analysis undertaken could have been extended almost indefinitely, there would seem to be no point in carrying out further work, for (1) every kraal we have visited in the Transvaal, Natal, Bechuanaland and Swaziland, used iron pots or occasionally paraffin cans ; and (2) although iron kaffir pots are stated to last for several years, the local manufacturers estimate that their sale reaches half a million each year, — sold to a Bantu population of about 8 million. The widespread commonness of a high iron intake is therefore incontestible. Obviously, the level of iron intake depends on many factors,— seasonal and economic availability of foodstuffs, individual preferences, type of cooking utensils used, methods of preparation, appetite, and so forth. We do not, therefore, wish to attach too much importance to our actual figures ; but consider ourselves justified in believing, as mentioned in an earlier communication (WALKER and ARVIDSSON, 1950), that the iron intake of the South African Bantu is far higher than that of Europeans, that the intake often exceeds 100 mg. per diem, and occasionally even double that figure.

What is likely to be the physiological effect of these frequent very high intakes of iron? Evidence to be described indicates that there is likely to be abnormal absorption of the element, which will be deposited and accumulated in various organs and tissues, thus giving rise to a particular type of siderosis.

Excessive absorption of iron arising from high intakes of the element. With intakes of iron derived from everyday foods, i.e. up to, say, 45 mg. per diem, the amount absorbed is regulated by the needs of the body (McCANCE and WIDDOWSON, 1937 ; GRANICK, 1946). Daily losses of metabolized iron through the kidneys and from the intestines are virtually nil (McCANCE and WIDDOWSON, 1937, 1943 ; HAHN et al., 1939). A small amount is stated to be lost in perspiration, though this is not agreed upon (MITCHELL et al., 1949 ; FINCH et al., 1950 ; PEROSA et al., 1951). The drain from menstruation approximates to about 1 mg. per diem when spread over the whole whole cycle (FOWLER and BARER, 1936). Hence, the amount of iron required to be absorbed to replace these losses is only a few mg. per diem.

With a high intake of iron, however, (such as occurs during iron therapy or, as in the present instance, from an adventitious source of the element), the regulatory mechanism described above no longer operates effectively, and considerable amounts of iron may be absorbed. Such iron is retained and not excreted (McCANCE and WIDDOWSON, 1937, 1943). Little attention has been paid to this excessive retention in recent reviews on iron metabolism (GRANICK, 1949 ; HYNES, 1949 ; DARBY 1950 ; PIRRIE, 1950 ; LANCET, 1951). Examples to illustrate the retention are given in Table V.

With the normal or non-anaemic subjects the data given confirm the conclusion reached by earlier observers, such as QUECKENSTEDT (1913), that with intakes of iron greater than are supplied with everyday foods, an abnormal amount is retained by subjects who are not in need of the element. Observations on one of the non-anaemic female patients of BROCK and HUNTER (1937) are illuminating, for presumptive evidence indicates that she retained almost 8 g. iron during the 57 days when iron salts were ingested in therapeutic doses.

Although primarily concerned with the response of normal subjects, it is interesting to note that while patients with hypochromic anaemia would be expected to make good their deficiency of iron in the presence of an ample supply, yet, in the studies cited (Table V), far more iron was retained than was required to restore haemoglobin levels to within normal limits. This finding, using radio-active iron, has been confirmed by DUBACH et al., (1948). Regarding the amount of iron retained,— the information given on Subject I of FOWLER

TABLE V. Retention of iron from high iron intakes.

Authority	Subjects	Period of observation (days)	Iron intake (mg./day)	Total iron ingested (g.)	Total iron retained (g.)
Normal or non-anaemic subjects					
Brock and Hunter (1937)	2 females 2 males ages 7-30 years	6-10	0.538-2.409	3.228-21.680	0.343-1.034
Widdowson and McCance (1937)	2 females 2 males ages 21-29 years	36-46	0.975-1.371	44.850-61.432	1.510-5.031
Gram and Leverton (1951)	82 females ages 18-42 years	14*	0.110	1.540	0.125-0.175
Subjects with hypochromic anaemia					
Brock and Hunter (1937)	4 females 1 male ages 16-55 years	9-12	0.374-1.253	3.366-11.280	0.639-2.491
Fowler, Barer and Spielhagen (1937)	6 females ages 21-46 years	6-29	0.170-0.244	1.020-4.930	0.157-1.480
Fowler and Barer (1937)	9 females 1 male ages 26-49 years	6-54	0.500	3.000-22.000	1.088-8.854

* Period of treatment 28 days, balance observations being undertaken during the last 14 days only.

and BARER (1937) suggests that during iron therapy she retained about 12 g. iron over a period of 94 days ; moreover, at the end of the period of observation long after her physiological needs had been met, she was still retaining iron at a high rate.

To summarize,— normal subjects, also anaemic subjects have been shown to retain an excessive amount of iron when ingesting abnormally high doses of the element. With the subjects observed, the amount retained reached several grammes. One concludes, therefore, that the usual response to an abnormally high iron intake is an excessive retention. In other words, under such conditions of intake, the regulatory mechanism, which is so effective with everyday levels of intake, (i.e. the "mucosal block" of GRANICK (1946)), ceases to operate.

PREDICTION OF IRON OVERLOAD PICTURE IN SOUTH AFRICAN BANTU.

For abnormally high retentions to occur, it is essential that the iron intake must occasionally exceed the level where the mucosal block no longer operates satisfactorily. For white people, relevant information has been given by DEBACH et al. (1948), who studied the absorption of radio-iron in 10 normal subjects. Total iron intakes were maintained at 1 mg. per kg. body weight,— i.e. about 60-70 mg. for an adult male or female of average weight. Of the iron absorbed, the data given suggest that nine of the 10 subjects absorbed a portion of iron which was not utilized in haemoglobin formation, this portion averaging 7 per cent. of the iron intake. Unrequired iron, therefore, was "packed" into the body at the level of iron intake used. In addition, the balance observations of GRAM and LEVERTON (1951), given

in Table V, show that abnormal absorption occurred at an intake of about 110 mg. iron per diem. Such levels of intake are certainly higher than are usually encountered in practical nutrition, yet they are lower than often occur with the Bantu. Provided that the response of these people to a high iron intake is the same as that of white subjects, then it would seem inevitable that occasional abnormal retention results, with intermittent deposition and slow accumulation or overload of the element occurring in the body.

Bearing in mind the dietary habits of the Bantu, it is possible to forecast what should be the consequences of the overload.

(1) Abnormal deposition should be very common and widespread. Various observers (STRACHAN, 1929; GILLMAN et al., 1945a; HIGGINSON et al., 1953) have commented on the commonness of such deposition; the last-quoted workers have noted its occurrence in about half of all Bantu adults in Johannesburg examined at necropsy. Siderosis has been observed not only in Natives from the Union, but from the Rhodesias, Bechuanaland, Swaziland and Mocambique.

(2) It should be rare in the young, should affect males possibly more than females, and should increase with age. The above mentioned workers have shown that this is so.

(3) Abnormal deposition of iron should not be associated with any particular disease or state of health. GILLMAN et al. (1945a) found it almost equally common in patients with pellagra, with cirrhosis, and in subjects dying from trauma and enjoying apparently good outward health. HIGGINSON et al. (1953), from examination of 296 necropsies, concluded that the primary disease bore no relation to the presence or extent of the siderosis observed.

(4) Occasionally the deposition should be very intensely displayed. GILLMAN et al. (1945a) found as much as 5.4 per cent. iron dry weight in the liver of patients,—50-100 times the average amount present in non-siderotic livers. HIGGINSON et al. (1953) have confirmed this finding; moreover, they have found as much as 10.5 per cent. iron in a spleen—about 70-80 times the average amount normally present.

(5) Concerning the morbid anatomical distribution of iron in iron overload, there are no data published for man. But various studies have been undertaken on animals and the combined evidence shows that in severe experimentally-induced iron overload, the spleen is most affected, followed by the liver; smaller concentrations are found in the kidney, but only traces in the pancreas, thyroid and heart. The animals studied include mice (CAPPELL, 1930), rats (KINNEY et al., 1949; HEGSTED et al., 1949; FINCH et al., 1950), rabbits (ROUS and OLIVER, 1918; POLSEN, 1933) and dogs (FINCH et al., 1950; BROWN et al., 1950). This pattern of distribution is precisely what is observed chemically and histologically in Bantu siderosis (HIGGINSON et al., 1953).

(6) Hypochromic anaemia should be very rare in a population with high iron intake and high reserves of the element. Several local observers (SQUIRES, 1949; MURRAY, 1953; FOY and KONDI, 1952) have testified to the extreme rarity of this type of anaemia.

(7) Increase of iron in the serum should be occasionally observed when iron stores are very excessive, as in haemochromatosis and transfusional siderosis (SHELDON, 1935; KARK, 1937). Such increase has been reported among the Bechuanaland Bantu by SQUIRES (1952). His observations have been confirmed by GERRITSEN and WALKER (1953a, c) who found serum iron values often exceeding the figures reported for the above diseases. In certain groups (in contrast to haemochromatosis and transfusional siderosis), elevations of total iron binding capacity have been found, though in no case has saturation of the iron binding protein been observed.

(8) The validity of a habitually high iron intake and the presence of high iron stores in women may be checked by comparing their haemoglobin and haematocrit values at the beginning and end of pregnancy. LUND (1951) and BENSTEAD and THEOBALD (1952) found that when iron was administered to non-anaemic pregnant white women, no change was observed in the above two values, in contrast to the usual fall reported as pregnancy progresses. Interestingly enough, it has been found that on comparing the above data in the first and second half of the pregnancy period of Bantu women, no significant change occurs (GERRITSEN and WALKER, 1953b).

In all the above respects the predicted consequences of oral iron overload have been remarkably closely observed. It would seem reasonable, therefore, to consider that the habitually high iron intake of these people is the primary cause of the siderosis.

But there is, however, a number of conditions or states of ill health that promote or are accompanied by siderosis. These include :

(1) Iron administered intravenously;
(2) Causes other than haemochromatosis and malnutrition;
(3) Classical or idiopathic haemochromatosis; and
(4) Starvation or malnutrition.

(1) *Siderosis from iron administered intravenously.* Iron administered intravenously (either as iron salts or as haemoglobin) is retained and not excreted. In the Bantu, however, such therapy is so infrequent that its share in the responsibility for the siderosis can be neglected.

(2) *Siderosis due to causes other than haemochromatosis and malnutrition.* PETERS (1882) listed several diseases in which a measure of siderosis, usually mild, occurs. Contemporary textbooks on patholgy, that of BOYCE (1892), for example, referred to the siderosis present in pernicious anaemia, malignancy, cirrhosis, prolonged fever, and malaria. Among the Bantu, pernicious anaemia is extremely rare. Malignancy although not uncommon, is clearly not responsible for the commonness of abnormal iron deposition. Siderosis accompanying cirrhosis is reported to occur frequently among the white population(NEWMAN, 1933 ; HERBUT and TAMAMKI, 1946 ; ZIMMERMAN et al., 1950 ; KALK, 1950) ; but apparently, it does not occur, apart from the Bantu, in non-white cirrhotics. Among the Bantu, about half of the sufferers from cirrhosis show siderosis ; yet, the latter is often present to an intense degree in the absence of cirrhosis. On this account, GILLMAN et al. (1945a), do not believe that the cirrhosis and the siderosis (cytosiderosis) are related causally ; they prefer to regard the latter as a distinct entity.

Among the Bantu, the only common haemolytic disease is malaria which is endemic in many parts of Southern Africa. Of the four malarial livers examined by GILLMAN et al. (1945a), only small amounts of excessive iron were present. Moreover, very few typical malarial livers were observed in the cirrhotics, pellagrins, and others examined postmortem by these workers, who therefore concluded that malaria certainly could not account for the commonness of siderosis among the Bantu examined. SHELDON (1935) thought that the intravascular haemolysis from schistosome infestation might well account for the abnormal iron deposition among the Bantu ; GILLMAN et al (1945a), however, have shown that this view is untenable. Infection, septicaemia, and burns at first sight seem likely as a contributing cause of siderosis, for in the 36 siderotics detailed by GILLMAN et al. (1945a), these conditions were responsible for 11 deaths. But in many of the subjects, the amount of iron in the liver far exceeded what could be accounted for from destruction of erythrocytes. The infections, etc. mentioned in this section can, therefore, be regarded only as aggravational or conditioning factors.

(3) *Siderosis due to or accompanying haemochromatosis.* Among the Bantu, in common with many population groups inhabiting tropical and semitropical countries, hepatic enlargement and cirrhosis are frequently observed (GILLMAN et al., 1945a). When such occur simultaneously with abnormal deposition of iron, the diagnosis of haemochromatosis merits consideration (SHELDON, 1935). But HIGGINGSON et al. (1953) have noted many points of difference between idiopathic or classical haemochromatosis and the deposition of iron observed in the Bantu. The main points may be summarized as follows :—

(a) In the Bantu, iron storage occurs principally in the reticulo-endothelial system and liver; not until heavy deposits are present in the liver does the element appear in the epithelial tissues. This basic pattern continues to be observed, even in severe cases. By contrast, in idiopathic haemochrom-

atosis, iron storage, even in the early stages, is believed to be mainly parenchymal. In Bantu siderosis, a striking feature is the absence or only slight presence of pancreatic pigmentation; this contrasts with the heavy and invariable pigmentation of this organ in haemochromatosis.

(b) Hepatic fibrosis, invariably present in haemochromatosis, is often absent in siderosis in the Bantu, even in severe cases.

(c) Diabetes, present in four-fifths of cases of haemochromatosis, is very rare in Bantu with siderosis.

These and other points of difference lead to the conclusion that classical haemochromatosis* is not involved in the phenomenon so frequently displayed by the Bantu.

(4) *Malnutrition as a cause of siderosis.* Evidence from animal experiments will be described first. VIGLIANI (1931) found that when rats were starved or fed on a vitamin deficient diet, extensive deposits of haemosiderin were produced in the spleen, liver, and and lymph glands ; these deposits, he attributed to increased haemolysis.

More recently, the Harvard workers (KINNEY et al., 1949; HEGSTED et al., 1949; FINCH et al., 1950) have reported that when rats fed on an adequate diet to which 2 per cent. iron citrate (0.4 per cent. iron) was added, slight siderosis occurred. On a diet which contained 80 per cent. maize or rice and 20 per cent. lard, but without added iron, slight siderosis occured ; when, however, the supplement of iron citrate was included, the siderosis was greatly increased. Repetition of the experiments on dogs showed that they responded in a similar manner. In the rat experiments, it was found that the low phosphorus content of the iron-supplemented maize diet was primarily responsible for the abnormally high iron absorption ; for the latter could be reduced by adding phosphate salts to the diet. It is interesting to note, however, that prolonged feeding to rats of the main constituents of a common Bantu diet, consisting of maize meal porridge and sour milk, did not give rise to an excessive deposition of iron (GILLMAN et al., 1945b).

Another type of inadequate diet — one deficient in pyridoxine, — has been observed to increase the absorption of iron in both pigs and rats (CARTWRIGHT et al., 1944 ; GUBLER et al., 1949).

Evidence available from animal experiments thus shows that under certain conditions :

(a) particular types of inadequate diet allow an abnormal absorption of iron to occur;
(b) on such diets, excessive absorption may be greatly increased by a high intake of iron; and
(c) siderosis can occur on an adequate diet, provided the iron intake be raised to a sufficiently high level.

Among starved or chronically undernourished people, it has been observed that varying though apparently small amounts of haemosiderin are present in the liver (KEYES et al.,1950 ; MCCANCE et al., 1951 ; AOKI and NAKAMURA, 1952). In the Wuppertal study (MCCANCE et al., 1951), it was suggested that the presence of the iron pigment indicated the excess of the element (derived from haemolysis) over requirement. In the Japanese investigation (AOKI and NAKAMURA, 1952) the presence of the iron pigment was ascribed to intravascular haemolysis from tissue breakdown. Abnormal iron deposition has also been reported in the spleen of starved or chronically undernourished people ; here again, this result has been attributed to increased destruction of erythrocytes (KEYES et al., 1950 ; AOKI and NAKAMURA, 1952). In spite of the many relevant published observations referred to by the groups of workers cited, no data are available concerning the actual amount of iron abnormally deposited in any particular organ or tissue.

Under lesser conditions of deprivation, i.e. chronic malnutrition rather than under-

* In a previous publication, the term haemochromatosis was used erroneously; (WALKER and ARVIDSSON, 1950); the term haemosiderosis was intended.

nutrition, siderosis does not seem to have been reported. Where considerable excess of iron pigment present in, say, the liver of such people, the element could hardly be missed completely, for so many careful histopatholigical studies have been undertaken in Eastern countries ; e.g. in India (HUGHES, 1933 ; TIRUMURTI and RAO, 1934 ; VELIATH and SRINVASACHER, 1951), Ceylon (FERNANDO et al., 1948), Japan (SCHITKER et al., 1951) and Indonesia (STRAUB and SCHABERG, 1950). Absence of reports does not, of course, establish that intense siderosis does not occur among chronically malnourished people, but lack of evidence gives the impression that malnutition *per se*, is not responsible for the siderosis produced so markedly in the South African Bantu.

The finding that a low phosphorus diet promotes the absorption of iron in rats (KINNEY et al., 1949 ; HEGSTED et al., 1949), can scarcely have a bearing on siderosis in the Bantu, for the nature of their diet is such that their intake of phosphorus is unusually high (WALKER, 1951).

Although it is clear that the various conditions and diseases just discussed can cause or be accompanied by abnormal iron deposition, it is considered that they play little part in the type of siderosis under discussion.

While it would seem reasonable to suspect that the abnormally high iron intake of the Bantu is the primary cause of the widespread siderosis, before the authors' theory can be accepted it will be essential to establish that the people habituated to a high iron intake are precisely those in whom abnormal iron deposition occurs. This will obviously be a very difficult matter where individuals are concerned. If one deals with limited regional population groups, however, progress may be made in the following manner.

FACTORS DETERMINING THE OCCURRENCE OF IRON OVERLOAD IN AN AFRICAN POPULATION

Previous considerations concerning the iron intake factor have been general, so that it must be stressed that even in an area where it is usual for iron vessels to be used, and where fermented preparations are popular, a wide variation in the incidence and intensity of the overload occurring is to be expected. For, first, subjects, even when ingesting the same amount of iron, vary enormously in their individual capacity to retain the element (Table V). Second, fermented preparations, even when made within a particular locality, have been found to vary quite widely in iron content, according to the method of preparation employed. Third, even in an area where it is known that fermented preparations are popular, individual consumption habits naturally vary considerably. Fourth, the iron contribution from plant ashes and edibible earths consumed in parts of Central and Southern Africa (ORR and GILKS, 1931 ; BARKER, 1943), can make a big difference to the level of total iron intake.

Of the non-dietary factors, siderosis from haemolysis in malaria has been touched upon already. Available evidence suggests that, apart from severe cases, such siderosis is likely to be mild. Of much greater importance is the blood loss (and hence, iron loss), from parasitic diseases (GILLMAN and GILLMAN, 1950) which, in the African, occur mainly with hookworm and bilharzial infestations. In this laboratory it has been found that adults suffering severely from vesical schistosomiasis, have a blood loss much smaller than is usually supposed, a maximum of 6 ml. blood per diem was lost when eight subjects were observed over 10 consecutive days (GERRITSEN et al., 1953). With hookworm infestation, however, the position is different. Using data given by WELLS (1931) a relatively mild infestation of, say, 50 worms can give rise to a calculated blood loss of 40 ml., i.e. about 20 mg. iron per diem. We are

not satisfied with the validity of the equation used, and an investigation to study the actual blood loss in human patients with hookworm, using radio-iron, has been initiated. Nevertheless, it is well known that the chronic haemorrhage from hookworm infestation can cause severe hypochromic anaemia ; hence, in areas where hookworm infestation is common, the blood loss could nullify any tendency for iron overload from high iron intake. Hence, where hookworm infestation is widespread and severe, its presence is incompatible with frequent occurrence of siderosis. A further point to be considered is the bearing of siderosis on the incidence of iron deficiency anaemia. Abnormal iron stores, even in haemochromatosis, are available for haemoglobin formation (FINCH et al., 1950), so that where siderosis is common, iron deficiency anaemia should be rare. The converse to this statement is that according to studies undertaken by RATH and FINCH (1948), anaemia responsive to iron therapy cannot co-exist with siderosis.

The above points may be combined to serve as a test of whether, in a given region, iron overload is likely to be common or otherwise. Thus, if it can be shown that a high intake of iron prevails in an area, and that serious chronic blood loss does not occur, then iron deficiency anaemia should be rare and iron overload common and occasionally intense. Conversely, if in a given area infestation by hookworm is severe and widespread, and iron deficiency anaemia common, then iron overload should be rare, even in the presence of a high iron intake. The testing out of this generalization will be the subject of another paper, but the following examples illustrate briefly the manner in which it is hoped to apply the test in various regions south of the Equator:

Witwatersrand. The iron intake is frequently high (WALKER and ARVIDSSON, 1950). Parasitic infestation involving blood loss need not be reckoned with (de MEILLON, 1953). Iron deficiency anaemia is very rare (MURRAY, 1953; FOY and KONDI, 1952). Iron overload should therefore be very common—and this is the case.

Southern Bechuanaland. Our iron determinations undertaken on prepared foodstuffs, and also on stools, indicate that the iron intake is frequently high. According to de MEILLON (1953), the incidence of hookworm is low. SQUIRES (1949) and FOY and KONDI (1952) maintain that iron deficiency anaemia is rare. The phenomenon of iron overload should therefore be common. SQUIRES (1953) has noted that rust-coloured livers are seen occasionally at necropsy; livers of three adults examined at this laboratory contained 0.5-1.5 per cent. iron (dry weight). Of 10 young adult males coming to necropsy and recruited from Bechuanaland for service in the Gold Mines, histological evidence showed abnormal deposits of iron in nine of the subjects (HIGGINSON, 1953). Elevations of serum iron and total iron-binding capacity of the serum globulin have been reported among these people (SQUIRES, 1952; GERRITSEN and WALKER, 1953c).

Uganda. Fermented cereal preparations are made by the Natives. TROWELL and DAVIES (1951) state that while aluminium pots are favoured, both kaffir pots and paraffin cans are also used. These authors, however, have no knowledge of the iron intake of the general population. The important point is that hypochromic anaemia is probably the commonest pathological condition occurring among hospital patients, whose blood picture improves when they receive a small dose of iron (TROWELL, 1939; LEHMANN, 1949, 1951). Bearing these points in mind, then according to the authors' theory, siderosis in hospital patients coming to necropsy would not be expected to be evident. DAVIES and TROWELL (1951) maintain that such siderosis is not observed.

It is probable that the generalization employed over-simplifies the subject; nevertheless,

it is submitted that confirmation of the iron overload theory can be reached only by the accumulation of accurate information on the aspects discussed; and as previously mentioned, research work on these and other relevant lines is proceeding.

PATHOGENICITY OF SIDEROSIS

The final point to be discussed concerns the question of whether the presence of abnormally high iron stores is pathological *per se*. In various studies on mice (CAPPELL, 1930), rats (FINCH et al., 1950), rabbits (ROUS and OLIVER, 1918; POLSON, 1933), and dogs (FINCH et al., 1950; BROWN et al., 1950), experimentally induced severe oral iron overload has not caused cirrhosis, nor dysfunction of the liver, spleen, pancreas, or other organ. In man—the subjects referred to in Table V were known to have retained several grammes of iron; yet, no subsequent ill effects were reported. Furthermore, authoritative physicians of the past, like OSLER (1906), were emphatic that no ill effects attended prolonged iron therapy; the same view is held today, even though at present doses of iron are larger than they were in Osler's time (WILKINSON, 1950). In the Bantu, there is no evidence to show that the iron overload is detrimental to well-being. While it cannot be excluded that the presence of excessively high iron stores is ultimately pathological, current evidence provides no support for this possibility.

SUMMARY

(1) Among the South African Bantu, the intake of iron is often very high—as much as 200 mg. per diem. This high intake is due mainly to the uptake of the element from iron utensils occuring during the preparation of their usual foods (particularly fermented cereal products).

(2) Published experimental evidence suggests that this level of iron intake is sufficiently high to overcome the " mucosal block " or the regulatory mechanism operating at everyday levels of intake, and allow unrequired iron to be absorbed, deposited and accumulated in the organs and tissues of the body.

(3) Observations by several workers show that excessive deposition of iron does, in fact, occur frequently; and that the incidence, age and sex affected, the morbid anatomical distribution of the element, and other characteristics, are all such as might be predicted to arise from oral iron overload.

(4) Although several conditions can cause or be accompanied by abnormal iron deposition—discussion suggests that intravenous iron, excessive destruction of erythrocytes, idiopathic haemochromatosis, and malnutrition, play little part in the siderosis observed in the Bantu.

(5) It is submitted that the abnormal deposition of iron in these people is due primarily to their habitually high iron intake. No lesion of the digestive tract or any other organ need be invoked to account for it. Furthermore, there appears to be no evidence that iron overload *per se* is detrimental to well-being.

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" BANTU SIDEROSIS "

SIR,—We have been much interested in the paper by Dr. M. Gelfand on Bantu siderosis in Southern Rhodesia (*Transactions*, **49**, 370), since we have also carried out several studies on this subject in South Africa. Dr. Gelfand has found much the same anatomical distribution of iron as we have noted here, namely, the concentration is high in the spleen and liver, yet low in the heart, pancreas and suprarenals. Dr. Gelfand also confirms that there is no correlation between presence or degree of siderosis and clinical state.

There are, however, a number of points raised by Dr. Gelfand which we would like to comment on.

Iron pots. The mere use of iron pots for food preparation is insufficient to cause siderosis. In our view, the main causative factor in iron " overload " in the Bantu is the large consumption of acid fermented cereal foodstuffs prepared in iron vessels, whereby the total iron intake is raised to as much as 200 mg. per diem.

Maize. Despite conclusions reached from various studies on rats and other small animals, we consider that in man there is no satisfactory evidence that the type of cereal consumed is relevant to the causation of the siderosis.

Absence of siderosis in Uganda. Dr. Gelfand quotes us as saying that " the rarity of siderosis in Uganda would appear to be due to the fact that this excessive iron loss " (from parasitism) " is counterbalanced by a high iron intake." What we maintained was, that in Uganda the important point is that iron deficiency anaemia is very common, and that, as expected, siderosis is not observed. The precise position, however, cannot be discussed satisfactorily until the habitual range of iron intake of the Uganda Bantu is accurately known.

Hypochromic anaemia and siderosis. Dr. Gelfand rightly quotes us as believing that where siderosis is common, hypochromic anaemia is rarely found. American and British workers have clearly shown that anaemias in which haemosiderin is observed in the bone marrow do not respond to iron therapy. (In an unpublished study, we have described a close correlation obtaining between hepatic, splenic, and vertebral body iron concentrations). In our series of 1,500 postmortems and of about 500 liver biopsies, in only one instance have we noted siderosis in a patient suffering from hypochromic anaemia, but whose response to iron therapy we were, unfortunately, unable to study. Dr. Gelfand refers to the commonness of hypochromic anaemia in Africans in Southern Rhodesia ; we would be most interested to know what information he has on patients with co-existing hypochromic anaemia and siderosis, and of the nature of their response to iron therapy. In South Africa, hypochromic anaemia is not common, either among local hospital populations, or among numerous groups of men, women, and children studied in several rural regions who were not in hospital.

Siderosis and bilharzia. We do not agree that bilharzia, in the absence of hookworm infestation, is of relevance in siderosis. Our published studies of blood loss in bilharzia in adults, and, more recently, our unpublished studies on children, testify to the smallness

of the blood loss in such infestations. Furthermore, we have noted bilharzial infestation in about a quarter of Bantu adults in whom siderosis was present.

The causation of siderosis. Dr. Gelfand has reservations about the validity of the iron " overload " hypothesis. His quotation from Whitby is not apposite, for the latter was referring to every day levels of iron intake, and not to therapeutic or excessively high levels. Briefly, the iron " overload " theory rests on three cardinal points : (1) An abnormally high intake of iron is widespread throughout much of Southern Africa ; (2) A high iron intake (say over 100 mg. per diem) invariably causes a high absorption of the element ; and (3) such iron, once absorbed, is retained : excretion is negligible. Since (1) and (3) are incontestable, and since (2) has been demonstrated in all relevant studies (including radio-iron studies) yet undertaken, the theory cannot be otherwise than accepted. We are satisfied that the theory accounts for, or is in consonance with, the evidence on siderosis as seen in South Africa. However, like any other working theory, it will have to be rejected or modified upon the production of evidence which conflicts with it. In this connection Dr. Gelfand's observation of siderosis being common among Bantu infants and young children is most important, and it certainly is in contradiction to the " overload " theory, and is at variance with relevant observations in South Africa.

Siderosis in Bantu infants and young children. Histo-pathological and chemical studies by three independent groups of workers on the Rand have indicated the great rarity of siderosis in very young Bantu subjects. Determinations reveal Bantu livers to be low not high, in iron. Furthermore, despite elevated iron concentrations in maternal serum, we have not found elevated values in the iron concentration of Bantu breast milk. The thought struck us, is it not possible that infant hepatic iron compared with adult liver iron, is unmasked more easily ? In other words, is it possible for infant livers to give a positive Prussian blue reaction on naked-eye examination and yet have iron concentrations within the normal range ? To throw light on the question, we obtained livers from two Bantu infants who died at 10 days and 6 months respectively. Both gave a positive Prussian blue reaction within 5 minutes in the cold, yet the iron concentrations were 0.030 and 0.026 per cent. iron dry weight, respectively, values on the low side of normal range. Histo-pathologically, the negligible amount of haemosiderin noted in these two livers bore no relation whatever to the strongly positive naked-eye Prussian blue reaction observed on gross specimens. It is clear, therefore, that a naked-eye positive Prussian blue reaction on a gross specimen does not necessarily indicate siderosis in Bantu infants. In the light of these observations we do not regard Dr. Gelfand's findings as invalidating the iron " overload " theory. The Prussian blue test has significant value only if iron in all tissues and at all ages is equally demonstrable, when equally present. This aspect has not been investigated and can be solved only by studying under the conditions described, the relationship between naked-eye observation of Prussian blue reaction, histo-pathological assessment, and iron concentration determined chemically.

A. R. P. WALKER,
Human Biochemistry Research Unit,
South African Institute for Medical Research, Johannesburg,
and Council for Scientific and Industrial Research.
J. HIGGINSON,
Pathology Department, Baragwanath Non-European Hospital, and
South African Institute for Medical Research, Johannesburg.

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SIDEROSIS IN THE SOUTH AFRICAN BANTU

SIR,—At present, there is considerable interest in diseases and conditions characterised by iron excess. I would therefore be glad to be allowed to refer to certain aspects of the contribution by Golberg and Smith [1] on iron overloading and hepatic vulnerability.

In discussing the relevance of their experimental observations to human siderosis, they refer to siderosis in the South African Bantu. Regarding the ætiology of this phenomenon, they state, inter alia, " Gillman and Gillman [2] point to disordered metabolism of the hepatic cell; Walker and Arvidsson [3] draw attention to the heavy level of dietary iron. Both are partially correct. The amount of iron present in the liver is far too great to have arisen solely from disrupted mitochondria as the Gillmans assert, unless these mitochondria were loaded with iron in the first place; on the other hand, the dietary iron alone cannot adequately account for the enormously enhanced absorption from the intestine." As one responsible for the iron " overload " hypothesis on Bantu siderosis, I should like to challenge the latter part of this statement, and inquire upon what evidence their view is based.

First, regarding the amount of iron involved in siderosis in the Bantu, on the basis of Wainwright's [4] investigation in Durban, Bantu with *intense* siderosis (who incidentally form only a small percentage of Bantu siderotics) may gain about 10 g. excess iron over the period of say 10–20 years. This involves the accretion of 500–1000 mg. excess iron per annum, i.e., 1·5–3·0 mg. iron per diem. Now the balance studies of Fowler et al.[5] and of Gram and Leverton [6] show that iron intakes of the order ingested by the Bantu (up to 200 mg. iron per diem) are associated with absorptions far in excess of 1·5–3·0 mg. per diem. The findings in these studies are supported by recent investigations using radio-iron.

(1) Bothwell et al.,[7] in their observations on normal subjects given graded doses of iron, found that the mean amount of iron as ferrous salts absorbed ranged between 2 and 8 mg. as the dose was increased from 20 to 400 mg.

(2) Smith and Pannacciulli [8] summarised their recent investigation as follows: " Graded doses of iron from 0·001 to 300 mg., labelled with a tracer dose of Fe^{59}, have been given as a ferrous sulphate

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6. Gram, M. R., Leverton, R. M. *Fed. Proc.* 1951, **10**, 383.
7. Bothwell, T. H., Pirzio-Biroli, G., Finch, C. A. *J. Lab. clin. Med.* 1958, **51**, 24.
8. Smith, M. D., Pannacciulli, I. M. *Brit. J. Hæmatol.* 1958, **4**, 428.

solution to subjects without anæmia and to patients with iron-deficiency anæmia, and the amount absorbed calculated from fæcal estimations. The mean absorption in the subjects without anæmia decreased from 33 per cent. of the 0·001 mg. dose to 12·6 per cent. of the 100 mg. dose, and in iron-deficient patients from 50 per cent to 37·5 per cent., respectively. No limit to the total amount absorbed was reached, the total increasing to 12·6 mg. and 37·5 mg., respectively, from the 100 mg. dose in the subjects without anæmia, and in the iron-deficient group. A further increase occurred when 300 mg. were given."

(3) The St. Louis workers, Brown, Dubach, and Moore [9] have investigated the extent of the block to iron absorption produced by large doses of inorganic iron given several hours before a tracer dose tagged with ^{59}Fe. The finding most specifically relevant to the South African Bantu is discussed as follows : " The degree of block to iron absorption demonstrated in normal subjects is certainly inadequate to prevent the absorption of unneeded iron from the diet. One would have little difficulty, for example, in explaining the large tissue iron accumulation in Bantu natives, whose diet has been estimated to contain as much as 200 mg. of iron per day. Using figures derived from our observations on normal subjects, a ' block ' in the Bantu would reduce absorption from an expected 34 mg. to 23 mg. This would still yield an increment of iron for shunting to storage depots of 22 mg. in excess of the adult male's estimated daily requirement."

The foregoing studies concern the short-term response to a high iron intake by white persons unused to such an occurrence. There is no corresponding information on the Bantu—another race and habituated for years to excessive ingestion of this element. One must be cautious, therefore, over extrapolation. Nevertheless, I submit that there is no evidence against the hypothesis that the high iron intake of the South African Bantu can account for the enhanced absorption from the intestine, and for the siderosis so common among these people. This does not imply that the high iron intake is the only factor involved.

I also wish to refer to the statement of Golberg and Smith that " of the factors which may be concerned in Bantu siderosis, a low protein diet suggests itself ". I am not aware of unequivocal evidence on humans that favours this view.

South African Institute
for Medical Research,
Johannesburg.

ALEXANDER R. P. WALKER.

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9. Brown, E. B., Dubach, R., Moore, C. V. *J. Lab. clin. Med.* 1958, **52**, 335.

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Bone Marrow

On gross examination, the bone marrow, in cases with moderate and severe siderosis of the liver, was rust colored. Microscopic examination confirmed the presence of intracellular and extracellular iron pigment deposits. Numerous hemosiderin-containing macrophages have been observed also in marrow smears from Bantu patients. In one case of generalized idiopathic osteoporosis there was collapse of the vertebrae with fibrosis. The new fibrous tissue was very heavily infiltrated by iron-laden histiocytes.

Brain and Choroid Plexus

In no case was iron pigment found in the brain substance. On naked-eye examination the choroid plexus was of normal color and microscopically only minimal epithelial deposit was found in 2 of 4 very severe cases.

Voluntary Muscle

In 2 of 7 cases with severe visceral siderosis, very scanty pigment deposits were noted in the voluntary muscle of the tongue.

Lymph Nodes

According to the degree of hemosiderin deposition, the gross coloration of the nodes varied from normal to light brown or rust. On section, iron pigment first appeared in histiocytes lying in the medullary and subcapsular sinuses. In more severe cases, the deposits were both intracellular and extracellular. In some patients the nodes showed solid masses of hemosiderin granules, surrounding relatively normal lymph follicles (Fig. 11). Even in the most heavily affected nodes, fibrosis was not a feature.

The distribution of hemosiderin in the abdominal nodes followed a definite pattern. Those in the porta hepatis, pancreatico-splenic, and upper mesenteric groups contained the most iron pigment. The lymph nodes in the mesentery and those draining the doudenum and upper jejunum contained large deposits (Fig. 10), but those draining the ileum and colon, little or none; in mild cases, only the jejunal and duodenal nodes contained hemosiderin. In 3 cases examined, in which very scanty iron-laden macrophages were found in the jejunal mucosa, there were moderate pigment deposits in the corresponding jejunal lymph nodes and the nodes of the porta hepatis. In severe cases, heavy pigmentation was observed also in the glands of the lesser curvature and in the para-aortic group. In such patients, scattered

hemosiderin-laden macrophages frequently were noted also in the tracheobronchial, inguinal, axillary, and cervical nodes. The pattern of lymph node involvement was confirmed microscopically in 60 nodes, but in other necropsies the same pattern of involvement could easily be followed with the naked eye.

Lung

Hemosiderin deposits usually were scanty and limited to the interstitial tissues of the lung. In 4 cases with heavy liver pigmentation, large granules of hemosiderin were found obstructing some of the alveolar capillaries.

Other Pigments

In many livers a golden brownish pigment ("wear and tear" pigment) was found in the liver cells. This could be demonstrated by basic fuchsin. Iron was not demonstrated by the method used in this investigation. This pigment stained poorly or not at all with the periodic acid-Schiff's method, and it was sometimes sudanophilic even in paraffin sections. Although this pigment generally was more frequent with increasing age, the relationship was not absolute. Whereas hemosiderin was first found at the periphery of the lobules, this pigment was most marked at the center. In many cases the centrilobular cells contained "hemofuscin" but no hemosiderin, whereas at the periphery, iron pigment was present but no fuchsinophilic pigment. There was no correlation between the presence of this pigment and the degree of siderosis. A similar pigment which sometimes stained with the periodic acid-Schiff's technique was found in the heart muscle.

In addition, in many siderotic cases a further fuchsinophilic pigment was found. It was noted in the fibroblasts and macrophages of the portal tracts, the epithelium of the biliary ducts, the interstitial tissues of the pancreas, the capsule of the lymph glands and spleen, the myocardium, and in the smooth muscles of the blood vessels, muscularis mucosae, and myocardium (Fig. 11). It also was found occasionally in voluntary muscle, in the choroid plexus, and renal tubules. In case 25, the lymphatics of the submucosa were outlined by hemosiderin and fuchsinophilic pigment (Fig. 12). The color of this pigment varied from gray to brown in unstained paraffin sections. It differed from "wear and tear" pigment in that it was generally stained strongly by the periodic acid-Schiff's technique. Frequently it stained with Sudan black, even in paraffin section. It did not show iron. Its presence was variable and although usually most marked in severe siderosis this relationship was not absolute, in some cases little or none being found.

It must be emphasized that this pigment, although constantly fuchsinophilic, showed considerable variation in its staining reactions in organs from various parts of the body.

Although looked for in many cases, no ferrous iron was demonstrated in appropriately stained sections of the liver and spleen.

Discussion

In Table VI we have compared our observations on the major clinical and morbid anatomical features of Bantu siderosis with those in hemochromatosis and transfusional hemosiderosis as reported in the literature. For present purposes, idiopathic or classical hemochromatosis will be referred to as hemochromatosis.

Clinical Findings

According to the observations of Strachan,[1] Gillman and Gillman,[3,32] and from our present series, siderosis occurs very frequently in adult Bantu subjects examined at necropsy. It is rarely observed in the young, increases with age, and appears to affect males slightly more than females. The maximum incidence of hemochromatosis is in the fifth decade.

Diabetes mellitus was not common in our series. It is found in 78 per cent of the reported cases of classical hemochromatosis.[7] According to Brown *et al.*,[21] it has been reported in 5 of 40 cases of transfusional hemosiderosis.

Gross and Microscopic Findings

The general pattern of hemosiderin deposition in this series was similar to that reported by other local authors.[1,3,4]

On naked-eye examination, deposition of hemosiderin was most marked in the abdominal lymph nodes, spleen, liver, jejunum, and bone marrow, and was negligible or absent in the heart, pancreas, stomach, suprarenal and thyroid glands. The findings were confirmed by microscopy and chemical analyses in selected cases. The basic picture was that of storage in the liver and the reticulo-endothelial system.

The concentration of iron in the spleen was almost invariably greater than in the liver, even in mild cases. In hemochromatosis the iron content of the spleen is usually much lower than in the liver and concentrations of the degree observed in severe Bantu siderosis have not been reported. We have been able to find descriptions of only 2 cases of hemochromatosis in which the concentrations in both organs

TABLE VI

Comparative Features of Siderosis in the Bantu, Idiopathic Hemochromatosis, and Transfusional Hemosiderosis

	Siderosis in the Bantu	Idiopathic hemochromatosis*	Transfusional hemosiderosis‡
Incidence	Very common in the Bantu	Very rare	Very rare
Age	Increases with age	Maximum incidence in middle age	No specific age
Sex	Males affected earlier and more severely than females	Males:females = 20:1	No difference between sexes
Diabetes	Very rare	78% of cases	Has been reported
Hematologic picture	Normal	Normal	Associated with blood dyscrasias
Serum iron	Frequently abnormally high	Usually increased†	Usually increased
Liver			
Cirrhosis	Present in one fourth of severe cases	Invariably present	Portal fibrosis frequently reported
Weight	Variable	Usually increased	Variable
Iron content	High in advanced stage	High in advanced stage	Depends mainly on number and volume of transfusions
Pancreas			
Fibrosis	Rare and unrelated to degree of siderosis	90% of cases	Sometimes found
Hemosiderin	Present only in severe cases	Invariably present	Deposits sometimes found
Spleen			
Weight	Within normal limits	Increased	Variable
Iron content	Very high	Increased	High
Stomach	Usually no epithelial iron present	Iron usually found in epithelial cells	Sometimes found
Intestine	Much pigment in villi of upper small bowel	Slight pigmentation of villi	Not reported (not found in one case examined by us)
Heart	Iron pigment rarely observed	Hemosiderin present in 90% of cases	Sometimes pigmented
Bone marrow	Heavily iron pigmented	Little or no iron pigment present	Iron pigment occasionally observed
Type of iron distribution	Essentially in reticulo-endothelial system	Essentially parenchymal	Both systems equally involved

* Mainly after Sheldon.[7,26]

† Rath and Finch.[49]

‡ Abstracted mainly from Schwartz and Blumenthal,[11] Wyatt *et al.*,[12] Brown *et al.*[21]

were similar, namely, the cases of Bernoulli[7a] (cited by Sheldon[7]) and Vogt.[33] Several authors have emphasized the relatively small amount of hemosiderin found in the spleen,[7,21] and our findings are in agreement (cases 26 and 27). In 2 cases of transfusional hemosiderosis which we studied, the concentration of splenic iron was approximately equal to that in the liver (2 to 3 per cent). In animals which had received iron by injection, Polson[19] found a late reduction in the concentration of splenic iron after an early rise, due to increased storage in the liver. If, however, Bantu siderosis and hemochromatosis are considered basically similar conditions, it is difficult to explain the different concentrations of iron in the spleen on this hypothesis.

A striking feature of this series was the absence of pancreatic pigmentation in the majority of cases. Even when hemosiderin deposits were marked in the liver and spleen, the pancreas showed only scattered iron-laden interstitial macrophages; in only a few very severe cases was iron pigment seen in the glandular and islet cells and then usually only in traces. This is in contrast to hemochromatosis in which heavy iron pigmentation is invariably present, the iron content averaging 100 times the normal average value.[7]

The absence of significant hemosiderin deposits in the epithelial elements of the stomach, the thyroid, salivary, and suprarenal glands, and the myocardium is also in striking contrast to hemochromatosis where these organs are almost invariably pigmented.

Although slight hemosiderin deposits occur in the intestinal villi in hemochromatosis,[7] massive pigment deposition in the jejunal and the duodenal mucosa, as found in our cases, is not a feature. Such deposits, however, are noted in the intestines of rats and guinea-pigs which have ingested large amount of iron[23,34]; and in mice[16] and dogs,[6] after the injection of saccharated iron. Cappell[16] considered these deposits to arise from the re-absorption of intestinal iron which was of either dietetic or biliary origin. Such deposits have been reported in transfusional hemosiderosis in man,[35] but in many reports on this condition, no specific mention of intestinal pigmentation has been made. In one of our 2 cases of transfusional hemosiderosis, in which the concentration of liver iron was 2.58 per cent of the dry weight, no hemosiderin was observed in the jejunal villi.

It seems reasonable, therefore, to regard the upper portion of the small intestine as an area of high iron activity, possibly related to absorption. Further, where pigment deposits were large, the endothelial cells of the submucosal lymphatics often contained iron pigment, as did the corresponding lymph nodes (Figs. 10 and 13), and

relatively little iron was observed in the ileum or colon and their lymph nodes. On anatomical grounds, this suggests that these increased hemosiderin deposits were derived from active absorption in the small intestine, rather than by retrograde spread in the mesenteric lymphatics.

The fine portal fibrosis described in the liver of Bantu patients at all ages has been confirmed. Such tracts show varying degrees of fibroblastic activity and cellular infiltration. As the proportion of patients with cirrhosis in each decade does not increase markedly, these proliferative changes in the portal tracts probably may cease to progress at any age, and cirrhosis is not an invariable result. This is also the opinion of Gillman and Gillman,[32] who considered these changes nutritional in origin. In the majority of cases, this cirrhosis is of a fine multilobular type, fibrosis apparently being the dominant feature and not necrosis. Our findings are very similar to those of Vint[36] in East Africa.

All degrees of siderosis were found accompanying these various histologic patterns. Only one fourth of the cases with severe siderosis showed cirrhosis. In 7 cases with cirrhosis, hemosiderin deposition was absent, and conversely, 11 severely siderotic livers showed no significant portal fibrosis.

Gillman and Gillman[8] classified their cases of Bantu siderosis, first, by the degree of fatty changes in the parenchymal cells, and secondly, according to the distribution of hemosiderin in the liver cells, Kupffer cells, and portal tracts. They considered these types to represent various stages in the evolution of classical hemochromatosis. It is very doubtful whether fatty change in the liver can be related to siderosis which is usually first observed in the third decade, whereas the majority of fatty livers found by these authors among the Bantu were in patients with kwashiorkor, dying during the first 2 years of life. This has been our experience also. In Uganda, kwashiorkor with fatty liver is common,[37] but siderosis in adults is not observed.[38] In our series there was no relationship between pigmentation and fatty change, the latter appearing to be dependent upon the primary disease. We also have observed no correlation between the concentration of iron in the liver and the distribution in the parenchymal cells, Kupffer cells, and portal tracts. For these reasons we consider the absolute concentration of hepatic iron a better index of the evolution of Bantu siderosis than the pattern of pigment distribution in the liver. Further, in our opinion it is inadequate to base any classification of siderosis on the pattern in the liver without considering the general distribution in the body.

It is, of course, dangerous to dogmatize on the evolution of a disease from the static picture at necropsy. However, although slight deposits of hemosiderin have been reported in chronic bacterial diseases,[39] in the majority of our cases with slight or moderate siderosis, the pigmentation could not be so ascribed. We consider it reasonable to accept these as representing an early stage in the evolution of Bantu siderosis.

Cappell[16] showed that after the injection of saccharated oxide of iron in mice, the iron first appeared in the cells of the reticulo-endothelial system, and shortly after in the epithelial cells of the liver. On this account, and arguing by analogy from Cappell's experiments, we consider cases with only reticulo-endothelial involvement to represent the earliest stage in evolution. We also believe that the development of the morbid anatomical pattern in this series is very similar to that described in mice by Cappell. It is possible that the 8 livers in which parenchymal iron alone was present correspond to those livers in mice in which new non-iron-containing Kupffer cells have replaced the older cells. In Bantu siderosis, it appears that not until the concentration of iron in the liver cells and reticulo-endothelial system is high, can hemosiderin be demonstrated histologically in the parenchymal cells of the heart, pancreas, and salivary and thyroid glands. Although chemical estimation shows some increase in the iron content of these organs, this is probably mainly due to hemosiderin-laden phagocytes and extracellular deposits in the interstitial tissues. Epithelial hemosiderin deposits can, however, usually be demonstrated in the pancreas, thyroid and suprarenal glands, and heart when the concentration of hepatic iron approaches 3 per cent dry weight and splenic iron 5 per cent dry weight, approximately. In contrast, in cases of hemochromatosis, even when the concentration of hepatic iron is as low as 1 to 2 per cent dry weight, it is usual to observe considerable pigment in the parenchymal cells of the heart, pancreas, and thyroid gland.[7] In reviewing the distribution of iron in hemochromatosis, as described by Sheldon and later authors, we agree with Brown *et al.*[21] who considered that in hemochromatosis, storage even in the early stages is essentially in the parenchymal tissues. On the other hand, it appears to us that Bantu siderosis is mainly storage of excess iron initially throughout the general reticulo-endothelial system and in the liver cells. Iron pigment was not observed in this series in the parenchyma of organs other than the liver in the absence of heavy involvement of the reticulo-endothelial system. It is not possible, however, to distinguish between Bantu siderosis, hemochromatosis, or transfusional hemosiderosis by chemical or histologic examination of the liver alone. Although epi-

thelial deposits may be considerable, as illustrated by Gillman and Gillman[5] in Figures 156 and 167, and in case 25 of our series, we consider that the distinction from hemochromatosis can usually be made by the predominantly reticulo-endothelial involvement.

In transfusional hemosiderosis, the appearance of hemosiderin in the epithelial elements occurs at an early stage. This may be partly due to rapid overload of the reticulo-endothelial system because of the short period in which the condition develops. In some cases of transfusional hemosiderosis an identical pattern to that found in hemochromatosis has been described; in others the picture resembles our cases.[35] It is, however, possible that the degree of epithelial involvement in all three conditions may depend on the length of time during which they develop.

The relationship of cirrhosis and hemosiderin deposition has received considerable attention. The presence of increased fibrous tissue in the liver and pancreas in transfusional hemosiderosis has suggested that iron-pigment can produce fibrosis.[11] This view is not held by Wyatt, Mighton, and Moragues.[12] The histograms in Text-figures 1 and 2 show that there is a high incidence of severe hemosiderosis in cirrhotic cases. But of 7 livers with cirrhosis without hemosiderosis, 5 were from patients under 35 years of age, whereas all but 2 of the severely siderotic livers with cirrhosis were in subjects over 40 years. The frequency of both siderosis and hepatic fibrosis increases with age, and the apparent relationship may, accordingly, be fortuitous. Further, it is difficult to explain the lesser degree of siderosis observed in livers from female subjects, if fibrosis and siderosis are causally related.

As iron-laden reticulo-endothelial cells tend to migrate to the hepatic lymphatics,[16] there is possibly a tendency in siderosis for iron pigment to collect in enlarged portal tracts, causing the histologic picture seen in Figures 5 and 6. This might explain the correlation between severe cases of hemosiderosis and cirrhosis. On the other hand the degree of fibrosis in individual portal tracts was unrelated to the amount of iron pigment present in them. In some tracts, only a few iron-laden macrophages were seen; in other tracts in the same section, massive deposits were observed.

It has been stated that in hemochromatosis, fibrosis of the pancreas and spleen is a function of hepatic cirrhosis, and is unrelated to iron deposition.[40] Fibrosis of the spleen, lymph nodes, and intestinal villi was not a feature of our cases and there was no correlation between the degree of siderosis and pancreatic fibrosis, when present. Deposition of hemosiderin does not produce fibrosis in animals.[16,20,21] For these

reasons we agree with Gillman and Gillman[32] that fibrosis cannot be regarded as dependent upon hemosiderin deposition. Further, fibrosis and cirrhosis of the liver are commonly observed in other parts of Africa, where siderosis has not been reported.[36,38,41]

The classification of the non-iron-containing fuchsinophilic pigments in the body is difficult as they show a variety of staining reactions. In Bantu siderosis there is, however, a general increase in fuchsinophilic pigment. We agree, however, with Cappell[42] that the term "haemofuscin" is poorly defined and suggest that until these various pigments have been adequately classified they should be described according to their staining reactions.

ETIOLOGY

The hypothesis that siderosis in the Bantu is due to metallic poisoning[1] has received no confirmation. Sheldon[7] suggested that parasitic infestation may be responsible; but we regard this as unlikely, as has been shown by Gillman and Gillman.[3]

Gillman and associate workers[2-4,32] maintained that malnutrition and pellagra cause hepatic damage, with deposition of hemosiderin in the liver cells (cytosiderosis); later, this is followed by excretion of iron in the bile, with consequent reabsorption and widespread iron deposition (siderosis). Our post-mortem findings, however, indicate that iron deposition is widespread in the reticulo-endothelial system from the beginning, and division into two stages is not possible. Moreover, we wish to reiterate that it is unwise to isolate changes in the liver from those in the rest of the body.

If iron deposition was a feature of pellagra in South Africa, one would expect an approximately similar histologic picture in all cases of acute pellagra on admission to hospital, if the metabolic processes involved were similar in each. This was not reported by these authors, nor has it been our experience. Further, our liver biopsies from patients suffering from many different diseases have shown the same range of histologic pattern.

In undernutrition and starvation, hemosiderin deposits occur in both liver and spleen.[14] This is associated with general atrophy of the organs, and has been ascribed to breakdown of tissue. In our series, many patients were clearly not optimally nourished, but significant visceral atrophy was not observed, even on microscopic examination. In the Japanese series[14] the average weight of the liver was 900 gm., as against 1550 gm. in severe siderosis in this series. Further, one fifth of our patients with marked siderosis were apparently well nour-

ished. While undernutrition and infection may accentuate pre-existing siderosis in the Bantu, we do not consider these factors of major importance in the etiology of the condition.

It has been found that when mice, rats, and dogs are fed a corn grit diet, abnormal deposition of iron occurs, such deposition being aggravated by a high iron intake.[6,23,24] This phenomenon was found to be due almost wholly to a deficiency of phosphorus. We have been able to find no reports of such studies in man. In one case of hemochromatosis examined by Bothwell[43] no effect was noted on iron absorption by the addition of phosphates to the diet. It is doubtful, moreover, whether deficiency of this element could be involved in Bantu siderosis, since the high cereal diet of these people is rich in phosphorus.

Allusion has been made also to the observation that when rats, rabbits, and dogs ingest an abnormally large amount of iron, excessive absorption, retention, and deposition occur, even when the diet consumed is adequate. Walker and Arvidsson[44] reported that large amounts of adventitious iron are frequently present in the diet of the Bantu, as much as 200 mg. per day being ingested. Walker[45] considered that there is enough published experimental evidence in man to show that this intake is sufficiently high to permit unrequired iron to be absorbed, retained, and deposited in the body; and that this may perhaps account for the condition under consideration. Further information is needed, of course, on the effects of malnutrition plus high iron intake on iron absorption in man before this view can be accepted or rejected.

The etiologic fault in hemochromatosis is unknown. Sheldon[7,26] suggested that there is an inborn error of metabolism. Granick[46] put forward the hypothesis of increased iron absorption due to a greater reducing tendency of cells for iron. That such a high absorption does exist in some acute cases has been shown,[47] although this phenomenon may be secondary. Althausen *et al.*[48] did not consider malnutrition to be an etiologic factor. Despite these uncertainties, it will be apparent from evidence presented in this paper that the morbid anatomical pattern of hemosiderosis in idiopathic hemochromatosis is different from that observed in Bantu siderosis. This fact, together with the other points discussed, suggests that it is improbable that the two conditions are due to the same abnormality.

Summary

In the South African Bantu, siderosis is a common phenomenon.

Its morbid anatomical features and the pattern of iron distribution (histologic and chemical) have been described.

It has been suggested that iron storage occurs principally in the reticulo-endothelial system and liver and not until heavy deposits are present in this system does the element appear in the epithelial tissues. This basic pattern of storage in the liver and reticulo-endothelial system continues to be observed, even in severe cases. By contrast, in classical hemochromatosis, iron storage is believed to be mainly parenchymal.

The relationship of hepatic fibrosis to siderosis has been examined. It has been confirmed that varying degrees of portal tract fibrosis in the liver are a frequent incidental observation among Bantu patients. No constant correlation was found between the degree of fibrosis and the amount of iron pigment in the liver. Further, cases of severe siderosis were seen without cirrhosis, and conversely, cases of cirrhosis without siderosis. Fibrosis was not observed in other markedly hemosiderotic organs.

The possible etiology of the condition has been discussed. It is unlikely to be due to metallic poisoning or parasites; it is doubtful whether undernutrition, malnutrition, or pellagra can be regarded as major etiologic factors. The possibility of oral iron overload occurring among these people would seem to merit further investigation. Finally, the different pattern of iron deposition in idiopathic hemochromatosis and Bantu siderosis argues against these conditions having a common etiology.

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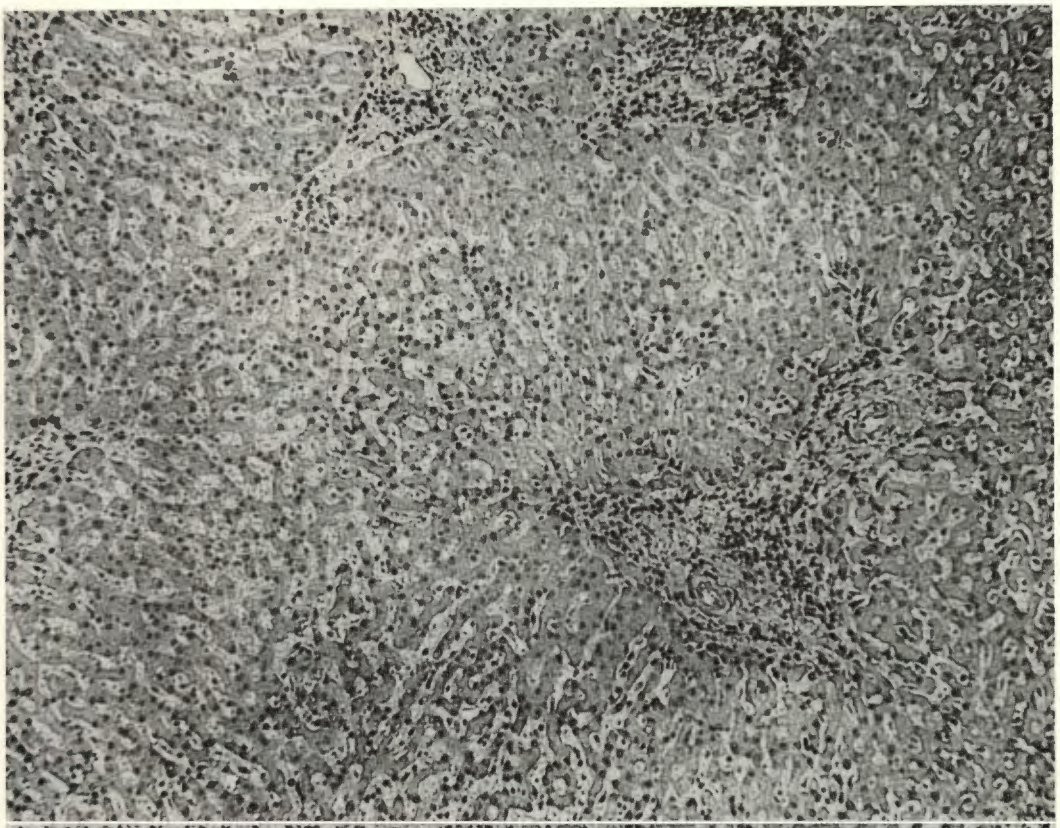
LEGENDS FOR FIGURES

Unless otherwise stated, all sections are stained for iron-containing pigment by hot potassium ferrocyanide and hydrochloric acid, and counterstained with basic fuchsin.

FIG. 1. Section of liver showing the slight portal fibrosis which is common among Bantu patients. Hematoxylin and eosin stain. × 105.

FIG. 2. Fine multilobular cirrhosis in non-pigmented liver. Hematoxylin and eosin stain. × 105.



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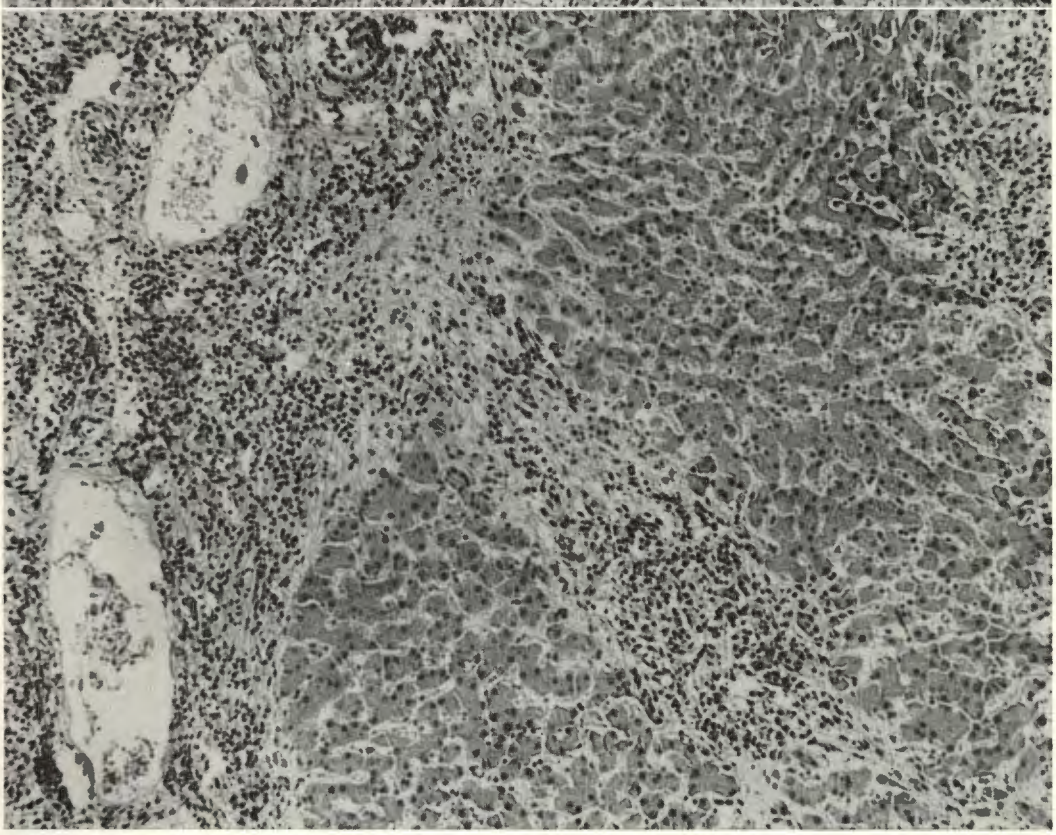

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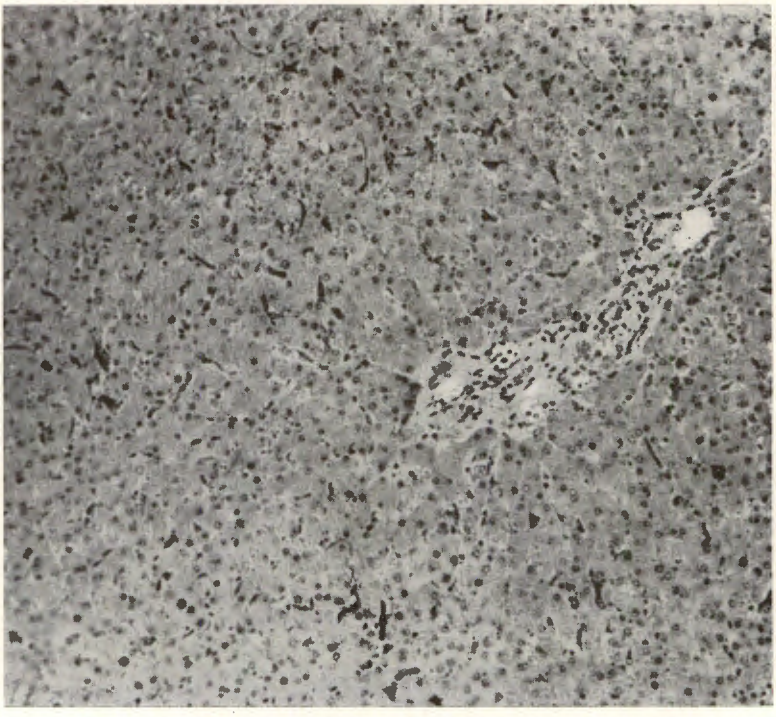
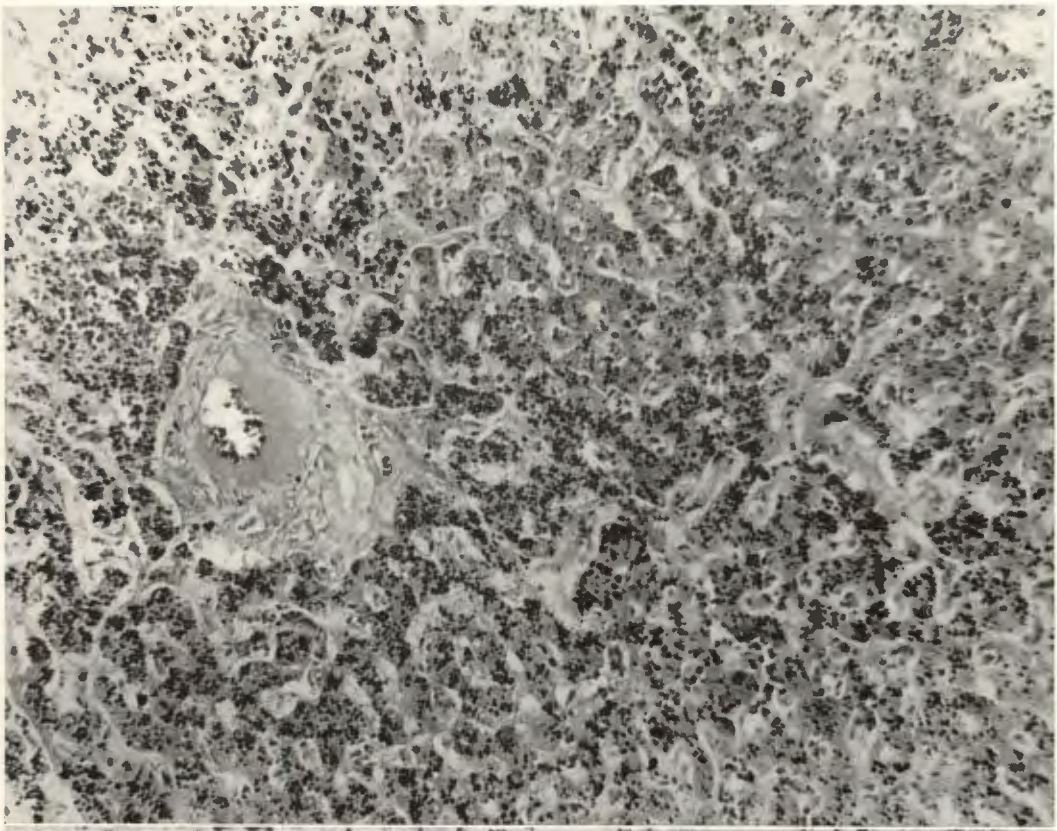
FIG. 3. Section of liver from case 14. Hemosiderin is almost entirely confined to the Kupffer cells. The spleen in this patient showed moderate iron pigmentation. × 140.

FIG. 4. Large hemosiderin granules filling the parenchymal cells of the liver. This liver was classified as structurally normal. × 180.

FIG. 5. This section shows Kupffer cells containing dense masses of hemosiderin lying in the sinusoids of the liver. In addition, heavy deposits of intracellular and extracellular pigment are present in the portal tracts. × 180.





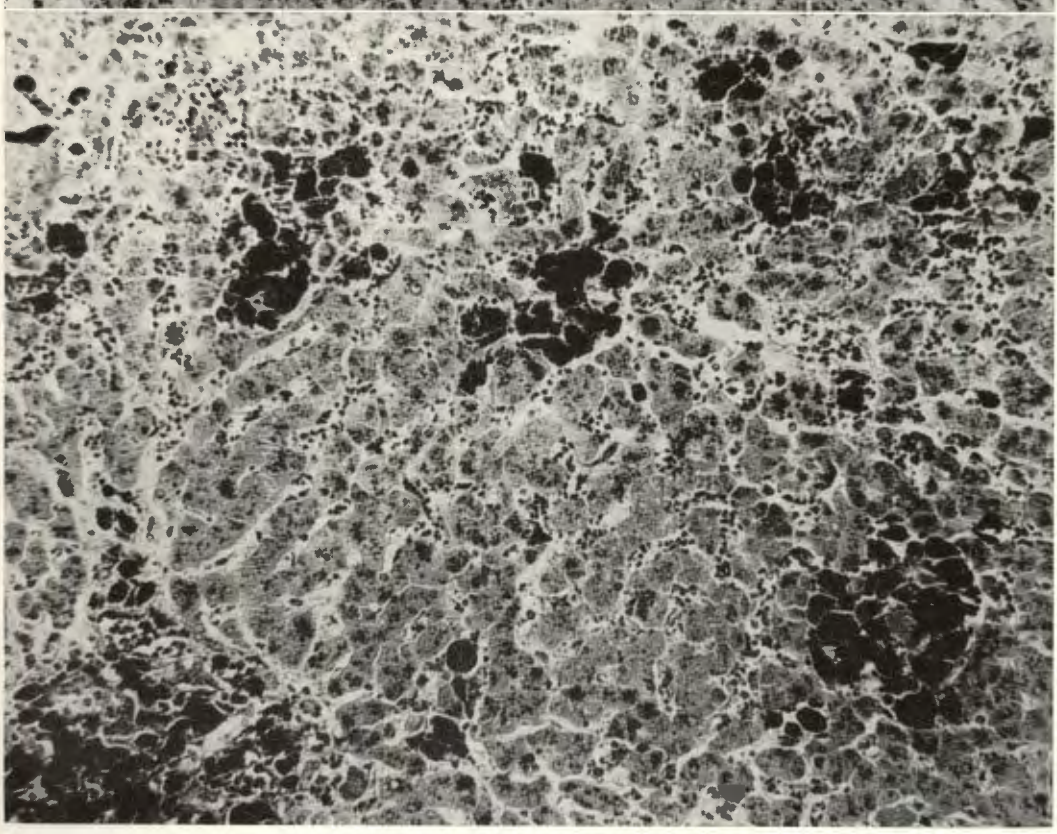
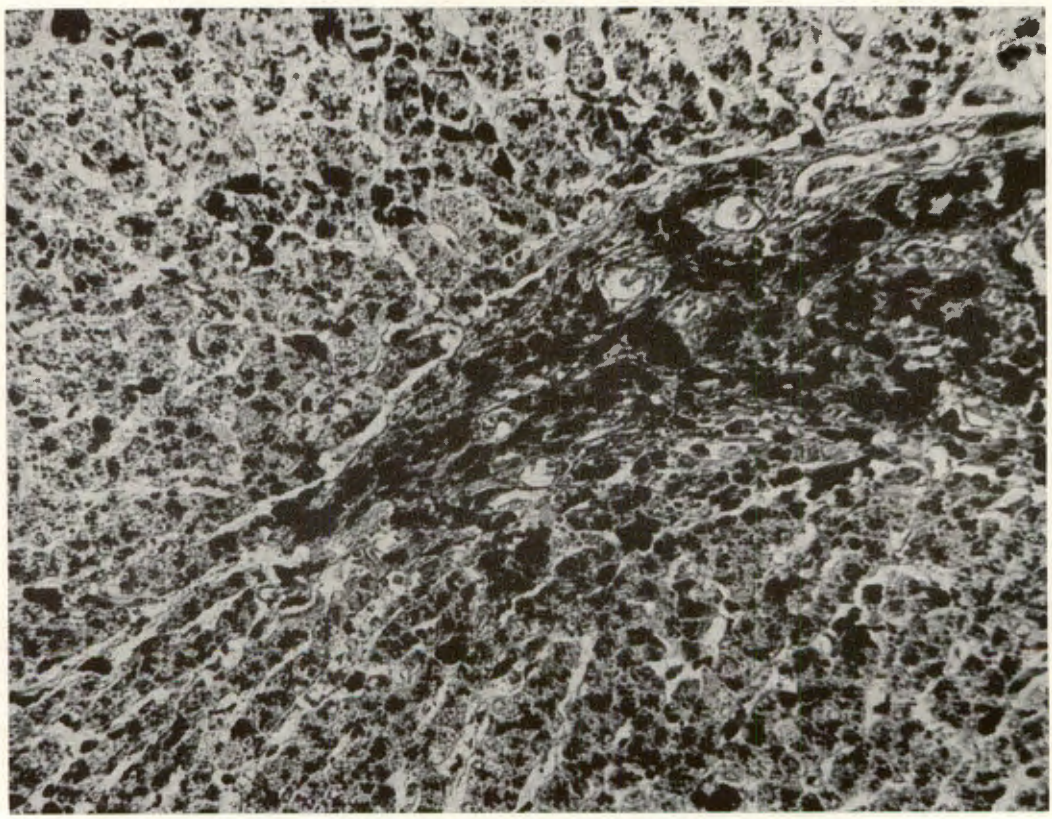
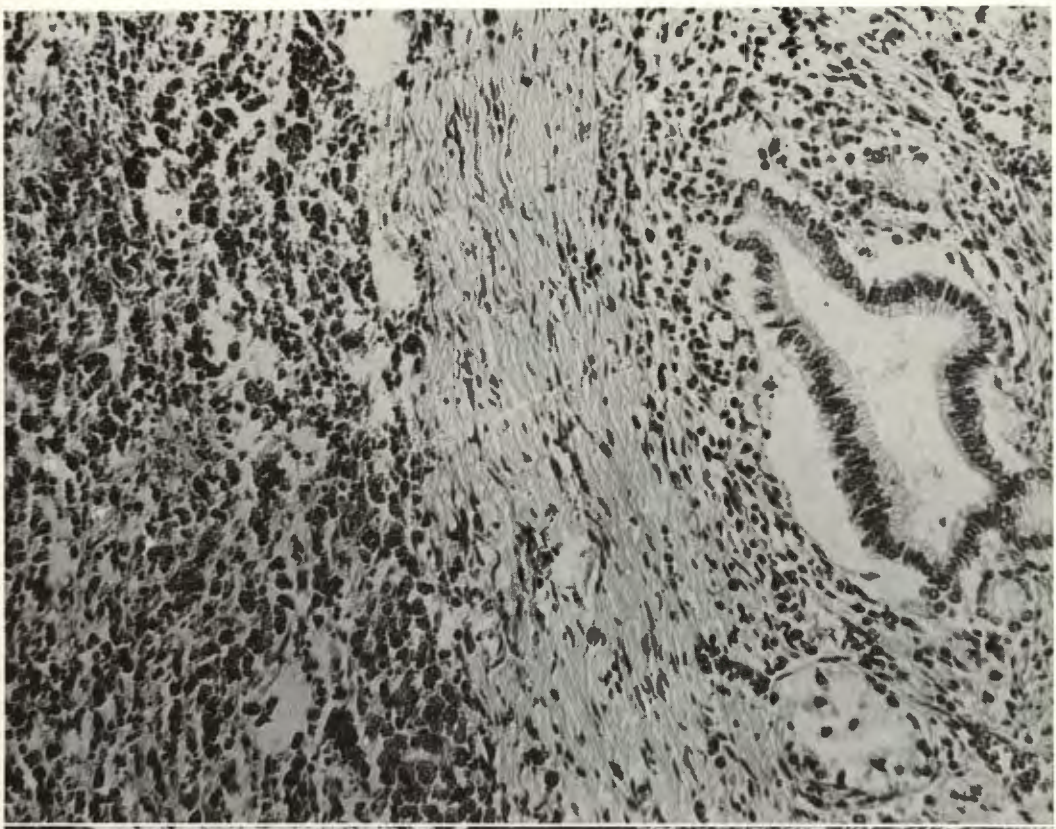


FIG. 6. Severe siderosis of cirrhotic liver (case 25). × 210.

FIG. 7. Infiltration of hemosiderin-laden macrophages into an area of fibrous scarring in the liver. Hematoxylin and eosin stain. × 210.

FIG. 8. Dense masses of hemosiderin in splenic pulp. × 210.





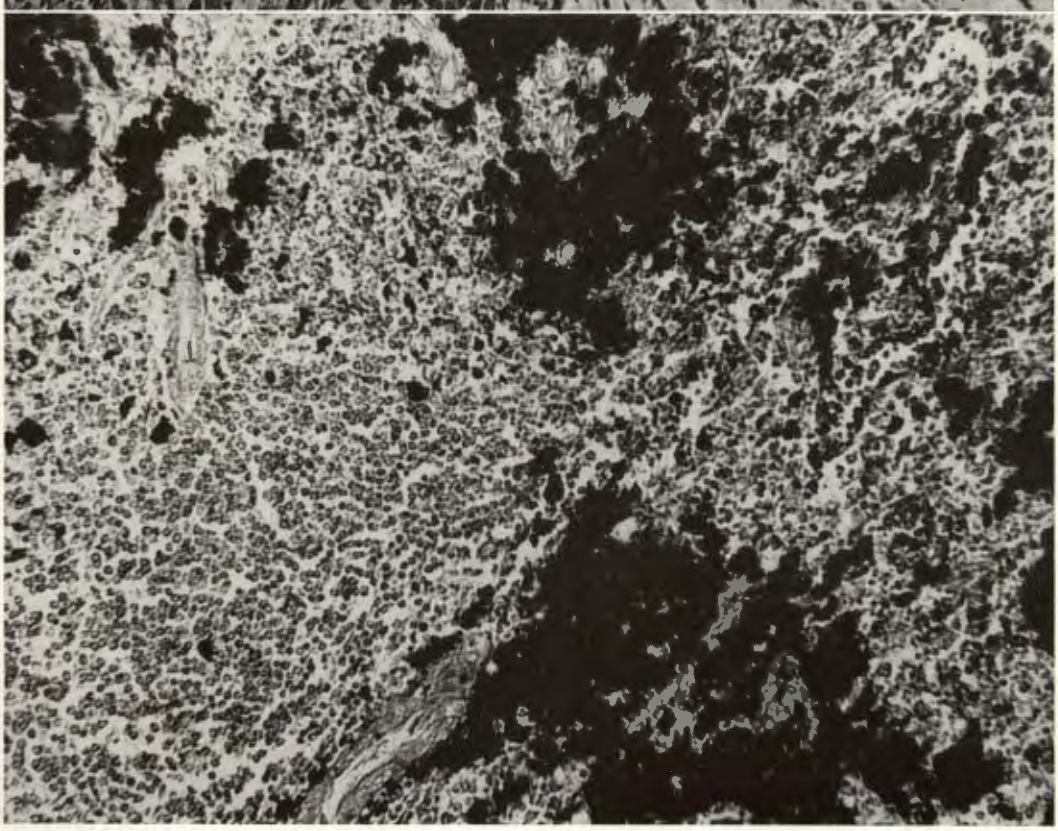
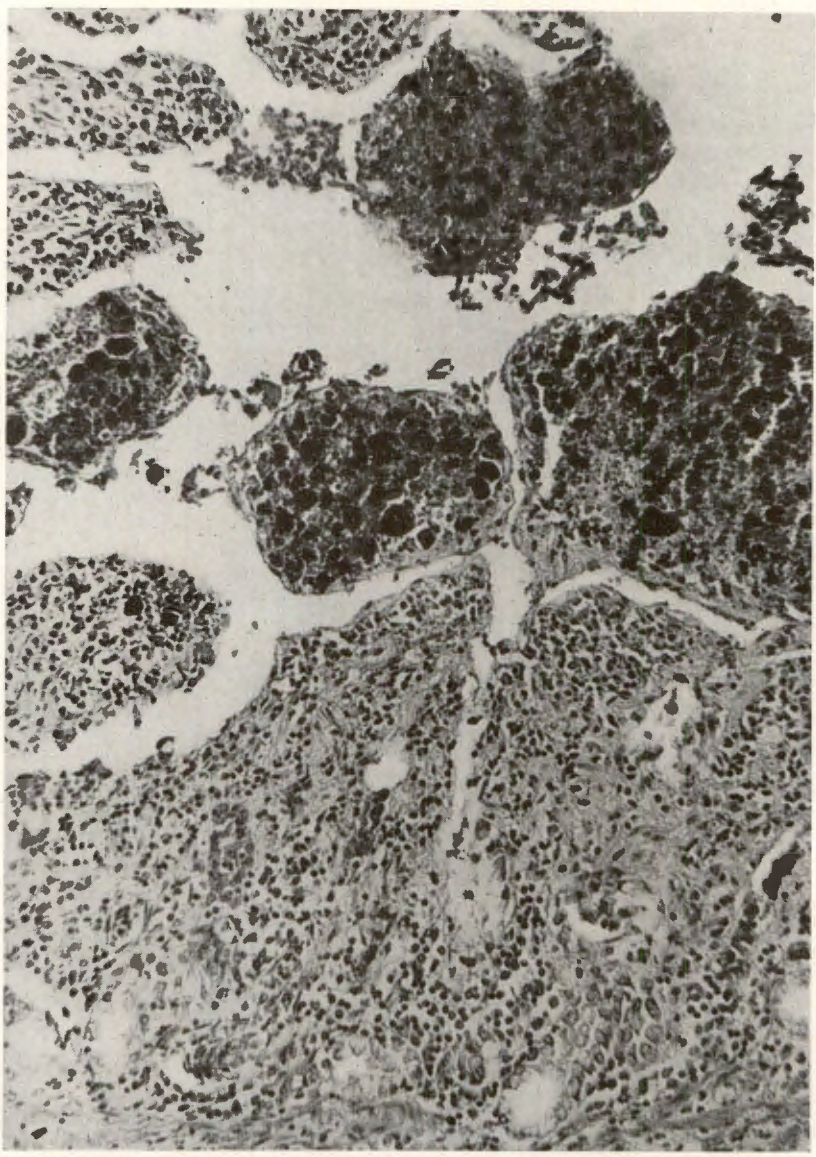
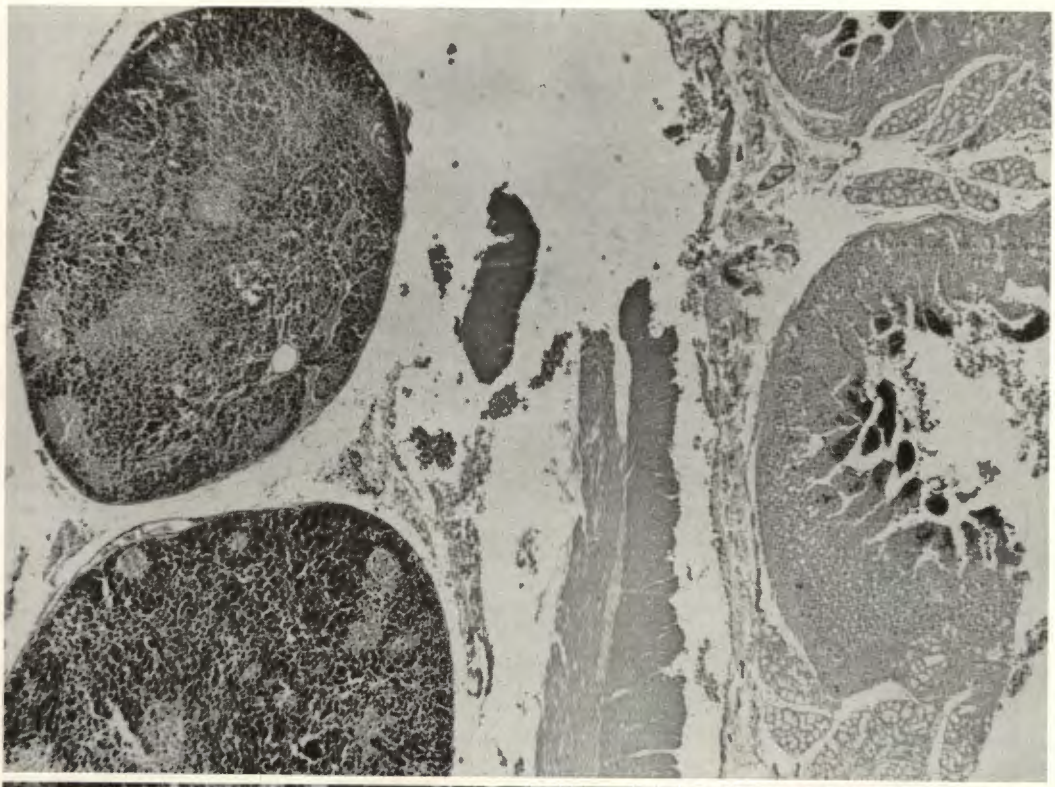


FIG. 9. Heavy hemosiderin deposits in substantia propria of duodenal villi. No pigment was found in Brunner's glands. × 180.

FIG. 10. Low-power view of duodenum and draining lymph glands. There are heavy deposits of hemosiderin in mucosa and glands. Same case as that from which Figure 9 was derived. × 20.

FIG. 11. Dense masses of hemosiderin in portal lymph gland. The lymph follicle is relatively unaffected. × 180.





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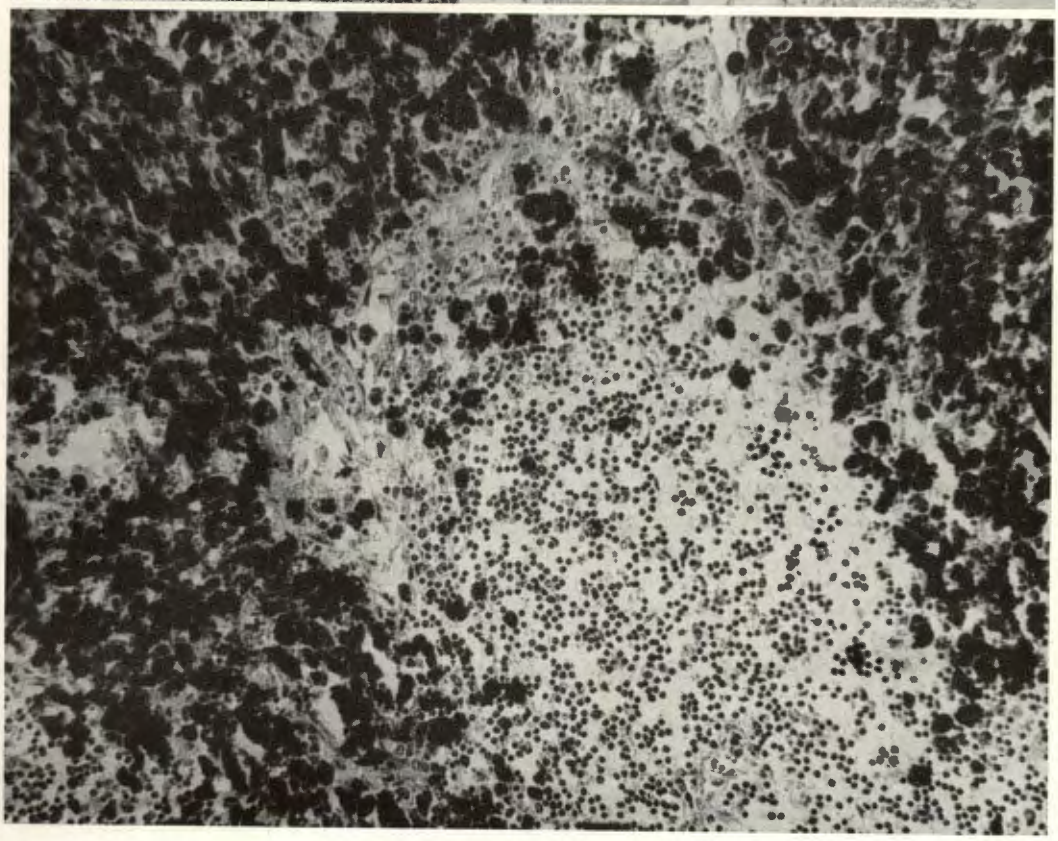

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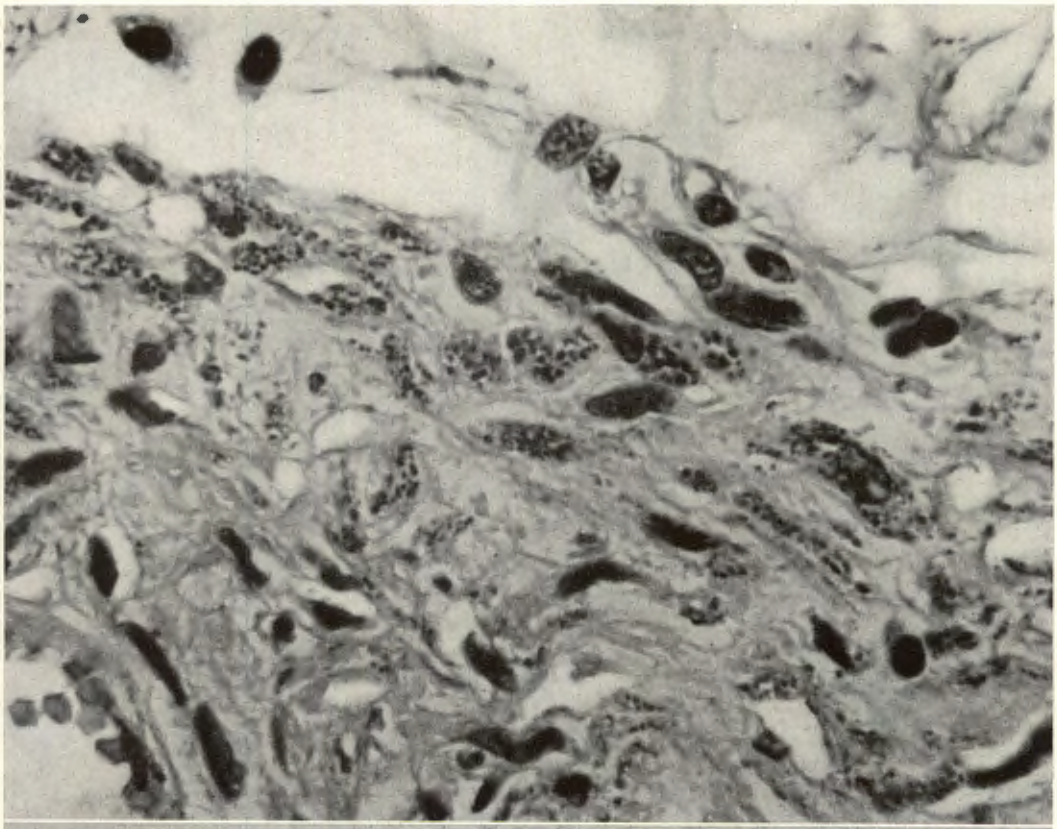
FIG. 12. Hemofuscin pigment in cells of muscularis mucosae of the stomach. Periodic acid Schiff's stain. × 1200.

FIG. 13. Submucosal lymphatic in jejunum. The pigment (A) is hemosiderin; the finer granules (B) are fuchsinophilic pigment. × 525.



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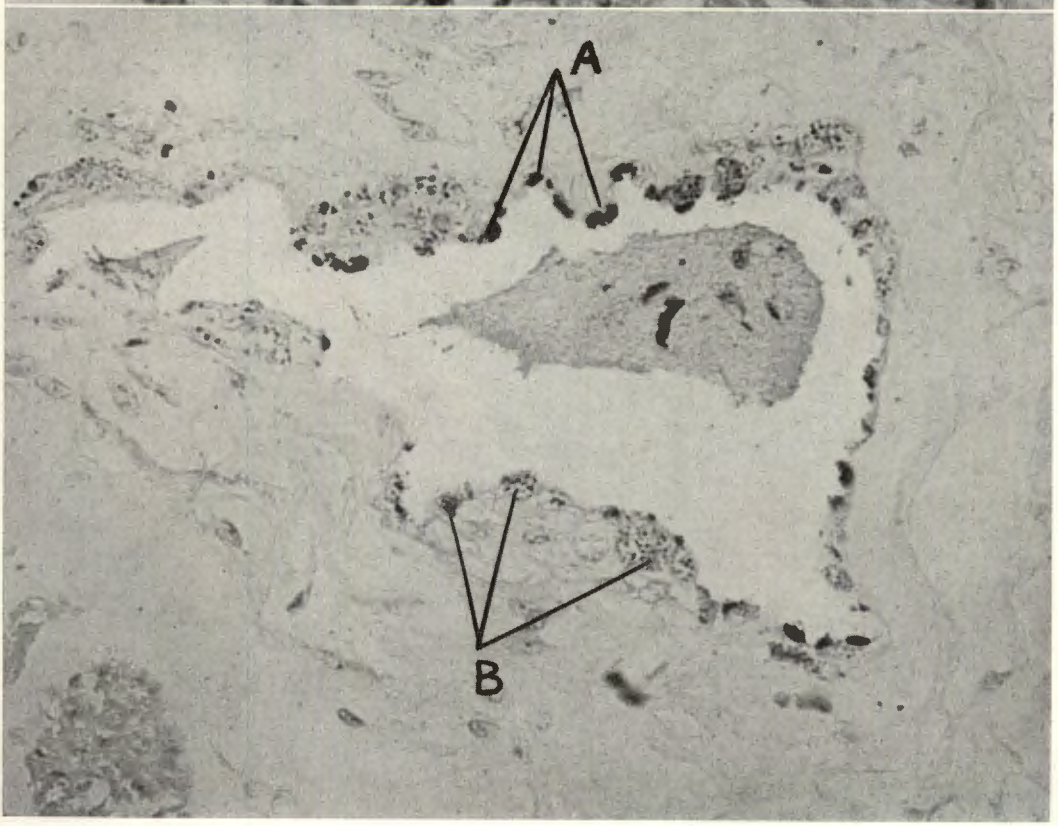

13

CORRESPONDENCE

HEMOCHROMATOSIS IN THE SOUTH AFRICAN BANTU

To the Editor: Their paper, "Hemochromatosis Terminating in Polycythemia and Hepatoma, with Observations on the Natural History of Hemochromatosis," by Jandl et al., which appeared in the November 14 issue of the *Journal*, alluded to the abnormal iron deposition or siderosis in the South African Bantu. Referring to the recent book by Bothwell and Finch,[1] these workers state, "Malnutrition and a high iron intake are common in the South African Bantu, who have a high incidence of a disorder similar to idiopathic hemochromatosis in the Northern Hemisphere." I should be grateful to be allowed to seek to put the local situation in better perspective.

High iron intake. There is no dispute that the diet of adult Bantu, intermittently, is very high in iron content,[2] and an ingestion of over 100 mg. *per diem* is common at weekends and on festive occasions. The sources of the adventitious iron are the iron vessels used in the preparation of fermented cereal preparations, particularly "kaffir beer" (derived from maize and "kaffir corn," *sorghum vulgare*).[2]

Malnutrition. As in many countries with large underprivileged populations, malnutrition is present to a certain degree especially among the very young. Among Bantu adults, malnutrition certainly occurs although it is less common than in populations in other parts of Africa and India that I have visited. The salient point that I wish to make, however, is that there is no evidence that malnutrition per se is a factor of primary importance in siderosis in the Bantu.[3] To quote from Bothwell and Finch,[1] "It has been postulated that the increased iron absorption is the result of a widespread metabolic defect induced by chronic malnutrition. There is, however, no firm evidence to support this contention and it is perhaps noteworthy that the degree of siderosis appears to be the same in apparently well nourished subjects." Recently, we have attempted to throw further light on this aspect by using urinary nitrogen partition (urea nitrogen to total nitrogen percentage, and urea to creatinine ratio) as a reflection of protein intake status, and elevation of serum iron as an approximate index of intensity of siderosis. First of all, we have found that groups of Bantu adults with approximately equally high iron intakes have equally high elevations of serum iron, even when wide differences in status of protein intake obtain. Secondly, we have studied groups of adults on roughly the same level of protein intake, but differing considerably in iron intake; the mean serum iron level was found to correlate with the mean level of iron intake. These results support the view that state of nutrition is not a major influencing factor in the occurrence of iron "overload." As I submitted many years ago,[2] and recently reiterated,[3] excessive iron intake is the primary etiologic factor in Bantu siderosis, and there is no need to invoke the existence or operation of other basic causative factors.

Distribution of iron in the body. In Johannesburg significant siderosis is present in about 70 and 25 per cent of adult males and females respectively.[4] In the large majority of those affected iron is confined to the liver and reticuloendothelial system.[5] But, again, to quote Bothwell and Finch[1]: "a small proportion of Bantu subjects do develop quantities of iron in the body of a similar magnitude to that found in idiopathic hemochromatosis, and when this occurs the distribution of iron is very similar to that found in the classical disease." In one study the small proportion referred to was approximately 3 per cent of adults studied at autopsy.[4]

Hemochromatosis in the Bantu. Diabetes is less common in Bantu compared with whites[6]; it is doubtful if the disease is present in more than 3 per cent of adults over forty years of age. One local clinical study has indicated that about a fifth or less of Bantu diabetic patients suffer from idiopathic hemochromatosis[6]; it should be emphasized, however, that this figure refers to a hospital population, and the incidence of hemochromatosis in the general African diabetic population may well be a good deal lower.

Briefly, then, although high iron intake and siderosis are very common in Bantu adults, only a small proportion have an iron distribution similar to that in hemochromatosis, and a still smaller proportion may be regarded as suffering from idiopathic hemochromatosis.

ALEXANDER R. P. WALKER, PH.D.
South African Institute for Medical Research
Johannesburg, South Africa

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Dr. Walker's letter was referred to the authors of the paper in question, who offer the following reply:

To the Editor: Dr. Walker's observations concerning iron overload in the South African Bantu have created considerable interest in the medical community for a number of years, and have had much to do with directing attention to unsuspected sources of dietary iron. We have not proposed that malnutrition necessarily affects the absorption of dietary iron, although it may well do so, but rather that malnutrition may affect the distribution of iron once absorbed, as is apparently true of megaloblastic anemia and folic acid deficiency, a situation frequent in patients with alcoholic cirrhosis.[1,2] Nor do we doubt that a high iron intake engenders an increase in body iron, for isotopic studies have made it clear that the more iron one ingests, the more one absorbs. Whether increased iron absorption per se causes hemochromatosis, however, is disputed. Our conclusion from the case reported is limited to the statement that some adults considered to have "idiopathic" hemochromatosis in fact have a combination of liver injury and high iron ingestion.

Other sources of local South African perspective have emphasized the prevalence of malnutrition in the Bantu.[3] Dr. Walker has emphasized the prevalence of dietary iron overloading. We have taken the liberty of assuming that the two situations may often coexist. When we spoke of a high incidence of hemochromatosis in the Bantu we considered a 3 per cent incidence to be on the high side. In the United States this would amount to about 6,000,000 cases rather than the 10,000 to 30,000 one would estimate on the bases, respectively, of post-mortem and ante-mortem surveys.[4]

JAMES H. JANDL, M.D.
CHARLES S. DAVIDSON, M.D.
WALTER H. ABELMANN, M.D.
RICHARD A. MACDONALD, M.D.
Boston

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