# THE
# INTER-RELATIONSHIP OF
# GASTRO-ENTERITIS AND MALNUTRITION
# IN CAPE TOWN.

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&

MY WIFE AND MY MOTHER

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# CHAPTER 1.

A review of the association of gastro-enteritis and malnutrition.

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## SUMMARY.


### THE INTERRELATIONSHIP OF GASTRO-ENTERITIS AND MALNUTRITION IN CAPE TOWN.

In the review of the literature special emphasis was placed on the association of gastro-enteritis and malnutrition. The highest reported morbidity and mortality rates are amongst infants and young children in communities where malnutrition is prevalent and socio-economic conditions are poor.

Because gastro-enteritis is a major problem in Cape Town, a study was undertaken to investigate the incidence of malnutrition and infection in children with severe gastro-enteritis. An attempt was made to determine the relative importance of these factors against the socio-economic background of the population concerned. The patients were followed-up for 1 year after the acute illness. The therapeutic effect of Penicillin and Sulphadiazine was compared with that of Chloromycetin palmitate. In an additional study the effect of a lactose-free diet was assessed in the treatment of severe gastro-enteritis.

The value of a low weight for age as an early sign of protein-calorie malnutrition was assessed. An association between weight deficit, stunting, retarded bone age and hypo-albuminaemia was demonstrated in children with gastro-enteritis, as well as in symptom-free children.

Gastric acid secretion was studied in a group of children with kwashiorkor and diarrhoea to determine the role of disturbed gastric function in the pathogenesis of gastro-enteritis.

From the above work it was concluded that the nutritional status of the patient was the most important single factor in determining the course of gastro-enteritis. An acute episode was most frequently precipitated by enteral infection.

In the management of gastro-enteritis it is essential to treat the malnutrition and not merely to treat the infection.

Prevention of malnutrition is an integral part of the prevention of gastro-enteritis.

## INTRODUCTION.

Diarrhoea is an important cause of illness throughout the world and remains a leading cause of death among infants and young children. The number of deaths from this condition is estimated at 5 million a year.[1]

There are important clinical differences in the disease as it manifests itself in previously normal wellnourished children compared with malnourished children.[2] The major part of the total world problem today is concentrated in the industrially underdeveloped countries where malnutrition and retarded development are a feature of infancy and early childhood. In a recent review Ordway[3] indicated the emphasis that is put on (1) the high morbidity and mortality rates among infants and young children, (2) the association with malnutrition, (3) the low socio-economic status of the affected population groups and (4) the multiple and often obscure aetiology of the disease.

In this review special emphasis will be put on the association of the disease with malnutrition, where morbidity and mortality are highest. Accurate morbidity figures are not always available but where mortality is high, morbidity is also high.

The industrially developed countries have experienced a rapid and consistent decline in diarrhoea mortality since the turn of the century. In 1952 the death from diarrhoeal disease was less than 10 per 100,000 of population in the U.S.A., Canada, Australia, New Zealand and the North-western countries of Europe.[2] In that year the death rate in New York City was 2 per 100,000 of population. This low figure was the result of a steady and progressive decline after the turn of the century which occurred throughout the United States and Canada.

During the same period a large fall in mortality was reported

from the United Kingdom.[4,5,6] Where 30,000 diarrhoea deaths were reported in 1900 there were only 891 deaths in 1951.[5] In Scotland in 1915 diarrhoea mortality was 57 per 1,000 births and in 1946 it was 8.5 per 1,000 births.[6]

The incidence of the disease has not always shown the same decline as mortality in these countries.[7,8] Diarrhoea remains a common cause of acute illness in children but few deaths occur as a result of it. Hardy[2] stressed the fact that in wellnourished previously well children diarrhoea is an acute illness with a tendency to recover completely within a few days.

In South Africa mortality from diarrhoea and enteritis amongst European (white) children is comparable to the above figures. In 1946 Brock[9] pointed out that diarrhoea was last on the list of causes of death for European children. A similar finding was reported by Robertson et al in 1956.[10] In 1961 European diarrhoea deaths were 1.1% of the total deaths at all ages and 6.5% of the total deaths in the age group 1-4 years in the Republic.[11] In the municipal area of the City of Cape Town in 1962 diarrhoea was not listed among the 10 most common causes of death in the European population.[12]

In the industrially underdeveloped countries diarrhoea mortality remains very high for the majority. Reliable figures for many of these countries are not available.

In 1952 diarrhoea was still the main cause of death in 9 out of 16 countries of the Americas.[2] In Mexico at that time diarrhoea deaths were still 300 per 100,000 of population although this figure was half of what it had been in 1931. Penido[13] reported that diarrhoea accounted for more than 30% of all deaths in 3 large Brazilian cities in 1958. This figure was as high as the total mortality from all other communicable diseases in children. Gastro-enteritis constituted the chief cause of death in Venezuela during the

period 1950-1954 in both urban and rural areas.[14] From Madras in 1954 Gopalan[15] reported diarrhoeal disease as the main cause of death next to respiratory diseases in children after the age of 1 month. Jelliffe[16] listed gastro-enteritis as the primary killing disease of tropical infancy in 1955.

In South Africa mortality rates from gastro-enteritis remain high amongst non-white infants and children.[9,10] In the first 5 years of life it overshadows all other causes of death and this is true especially between the ages of 1-4 years. In the whole of South Africa in 1961 there were 4,833 diarrhoea deaths out of a total of 13,321 deaths in Coloured children from birth to 4 years.[11] In Asiatics diarrhoea deaths were 222 of a total of 1,179 from birth to 4 years. Between the ages of 1-4 years gastro-enteritis accounted for 42.5% and 19% of all deaths in Coloured and Asiatic children respectively. In the same year the Coloured infantile mortality rate was 128.4 and the Asiatic 43.3 per 1,000 live births.[17] Figures for Bantu are not available because registration of deaths are totally unreliable for the country as a whole.

At a childrens' hospital in Cape Town in 1961 Ford et al[18] found that approximately 75% of all patients attending the outpatient department had diarrhoeal disease. At this same hospital during the period January 1963-June 1964 there were 625 deaths in the outpatient department.[19] Of these 314 died from gastro-enteritis, 130 from kwashiorkor, marasmus and malnutrition and 94 from respiratory tract infections. The next most common cause of death was measles which accounted for 10 deaths. More than half the deaths therefore followed severe gastro-enteritis and more than 40% of the rest died from severe malnutrition. These patients are drawn from the municipal and divisional council areas of Cape Town. Although it is the biggest childrens' hospital in the City, it is only one of six hospitals where large numbers of children are treated.

Kahn[20] and Truswell[21] stressed the vast discrepency between deaths in the white as compared with the non-white children, indicating that the latter figure is now comparable with the white death rate from gastro-enteritis 50 years ago. Although the discrepency between the races remains very large, a downward trend has been indicated in certain centres. In Johannesburg the infantile mortality rate in the Bantu has been halved in the past 50 years.[22] Within the municipal area of the City of Cape Town diarrhoea deaths have shown a steady decline since 1955.[12] This does not include the situation for the Divisional Council areas of Cape Town and surroundings where the most recent official figures are not available.

In any consideration of the problem of gastro-enteritis the factor of age incidence is of the utmost importance. The highest mortality rates are reported in the age groups under 5 years and are especially high under 2 years of age. In his review in 1960 Ordway[3] indicated that 70-85% of all admissions for diarrhoea were under the age of 2 years. Of these three quarters were less than 1 year old. In two villages in Guatemala only 17% of children less than 2 years old were free of diarrhoea for a year in 1956-57 and 54% of the 2-4 year age group had no diarrhoea during that time.[3] In Venezuela 78% of deaths occur between the ages of 1 month and 2 years while very few deaths occur after the age of 5 years.[14] In Israel the morbidity and mortality rates are high especially between 4 months and 2 years of age.[24,25] From Uganda Wilson et al in 1957 reported two thirds of their patients between the ages of 5 and 18 months[26]

In South Africa the majority of deaths occur under the age of 2 years when the disease also has the highest incidence.[20,27,28,29,30] Very few deaths occur after 5 years when the difference between the mortality rates of the various racial groups is no longer apparent.[10]

The vast differences in diarrhoea morbidity and mortality between developed and underdeveloped countries are mainly apparent between the ages 1-4 years. In the underdeveloped countries the highest incidence of the disease is between these ages and few cases occur in neonates. In South Africa in 1961 there were 3,071 deaths from diarrhoea in Coloured children under 1 year old. Of these only 140 were under 1 month old.[11] A similar low death rate was indicated by Gopalan from Madras.[15] In the developed countries the incidence of the disease is often highest in newborns.[6,31] If it occurs in older children it is mainly a problem of infection in institutions rather than a community problem.

A striking feature of the disease in underdeveloped countries is the strong association with malnutrition and the poor socio-economic circumstances of the affected groups. In the children involved the disease also presents a different clinical picture from that of the wellnourished.[2] It is frequently recurrent and an acute episode may initiate a progressive downward course. The lack of spontaneous complete recovery is considered an outstanding differential characteristic.

In the famous Wuppertal report McCance[32] indicated that diarrhoea has accompanied every famine in history and expressed the view that it is a product of prolonged undernutrition. Among German prisoners of war Park[33] in 1918 indicated a difference in diarrhoea incidence related to nutritional status. Well-fed people did not get diarrhoea while the malnourished not only got diarrhoea but died from it. In 1920 Marriot[34] postulated a theory in which malnutrition played an important role as a cause of diarrhoea. Hansen et al[35] recently stressed the fact that diarrhoea is almost invariably present in advanced states of protein-calorie malnutrition like kwashiorkor. They

reported a gradual return of stool weights to normal over a period of 2-3 weeks coinciding with a rise in serum albumin. The course was the same whether the stools had identifiable pathogens or not. It was suggested that protein deficiency possibly played a major role in the pathogenesis of chronic relapsing gastro-enteritis.

Further aspects on the role of malnutrition in the pathogenesis of diarrhoea will be discussed later. The frequency with which the disease occurs in malnourished infants and young children, the increased severity of the disease in such children and the association with poor socio-economic circumstances will first be reviewed.

In areas of low morbidity and mortality there are often considerable local variations between permanent residents and recent immigrants of poorer socio-economic standing.[2] From Israel two authors have indicated an inverse relationship of diarrhoea morbidity and mortality to the adequacy of the socio-economic environment and nutritional status.[24, 25] Significantly more deaths in the more grossly malnourished children with diarrhoeawere reported by Gomez et al[36] and De la Torre showed a stepwise increase in mortality with increasingly severe malnutrition in Mexico.[37] The relation of the disease to malnutrition has been reported for many countries in the tropics and sub-tropics,[16] from India,[15] the Phillipines[38] and Yugoslavia.[39] Chronic recurrent gastro-enteritis follows the same pattern in South Africa as elsewhere. Kahn[20] has shown the poor prognosis of the disease in malnourished patients and pointed out the high incidence in environments of poverty and poor hygiene. Diarrhoea morbidity was influenced by the nutritional status of the children in a study in Johannesburg where a similar relationship could not be demonstrated for respiratory diseases.[22] Krige[40] stressed the high incidence of the disease among children of migrant Bantu labourers in Durban. The outstanding

characteristics of this group were social disorganisation, poverty, slum living and ignorance. In Cape Town the gross degree of growth failure in fatal cases was strikingly demonstrated by Bowie.[30] Truswell[21,29] found 47% of severe cases and only 6% of the mild cases were malnourished. Previous workers concentrated on low weight for age and other clinical signs in assessing the nutritional status of their patients. Truswell[21] found additional evidence in the high incidence of hypo-albuminaemia in children with severe gastro-enteritis. Previous reports on serum albumin concentration were often less valuable because of the small number of patients studied[41] or a failure to indicate the state of hydration of the patient at the time of taking blood for analysis.[24] The considerable influence of dehyration on serum albumin[42,43] has been confirmed by Truswell.[21] Malnutrition existing prior to the onset of diarrhoea was demonstrated from a study of previous weight records of 300 fatal cases in Cape Town.[10] The poor dietary history of these low weight children would further support their weight deficit being dietary in origin. With every episode of diarrhoea they are in addition frequently starved for prolonged periods.[16,21,38] Diarrhoea is uncommon during the early months of life in the presence of proper and adequate feeding.[10,20,25]

Although sufficient data are not available to define the relative importance of contributory factors, the above data support the view that this type of diarrhoea occurs in primarily malnourished patients and that the clinical picture of the disease is different in the malnourished as compared with the wellnourished child.

The aetiology of gastro-enteritis is multiple and often obscure and views regarding the aetiology vary widely. Some would accept that diarrhoea in a malnourished child is merely a sign of his malnutrition while others would say that infective diarrhoea is the cause of his condition. It is not easy to

separate clearly the cause and effect of all the inter-related factors in such a complex disease. The production of clinical disease due to infections varies and depends on many factors. The virulence of the organism, the infecting dose, the interaction of more than one aetiological agent and the host response are only some of such factors.[8,44,45,46]

It has been agreed that diarrhoea, whatever its aetiology, is a more serious disturbance in the presence of malnutrition[3] and that many of the deaths attributed to gastro-enteritis are due primarily to malnutrition.[16] These concepts are of great practical importance in that the nutritional status of the patient seems to make the difference between mild and severe disease and even between life and death in response to an infection.

The chief precipitating cause of diarrhoea is usually stated to be an enteral infection[3] although this is not always identifiable.

Shigella, Salmonella and the Entero-pathogenic E.coli groups are considered the most important diarrhoea producing organisms. Other entero-bacteria like Proteus are of doubtful pathogenicity even if they are found more frequently in states of diarrhoea than in healthy persons.[47]

Shigella occurs more commonly in summer than in winter[20] and is most commonly found in the 1-5 year age group.[8,48,49] The younger the child the less likely is it to be a symptomless carrier.[8,3] Spread of the infection occurs mainly by contact with patients and infected articles.[8] The isolation varies greatly in diarrhoea outbreaks. From Uganda in one series[50] it was 12% and in another 25%.[26] In the latter study only 33% of cases had Shigella, Salmonella or E.coli. Hardy[2] pointed out that in Guatemala more cases were labelled as being of unknown aetiology than the total of those that had Shigella, Salmonella and E.coli. Friedman's study[24] in Israel had 4.5% of cases due to Shigella and

Salmonella. In South Africa the reported incidence varied between 14% and 30%.[20,51,52] In Cape Town in 1959 Watson and Mercott[53] found 17% Shigella and 3% Salmonella in a group of untreated patients with diarrhoea attending an outlying clinic.

Salmonella enteritis occurs mainly in infants and children[3,54] and has the highest death rate under 1 year old.[8] The incidence is rerely above 10%.[20,51,52] In a group of 31 kwashiorkor patients in Jamaica Jelliffe et al[55] found Salmonella in 6 patients with chronic enteritis. They considered this an important factor in initiating the nutritional breakdown. Isaacson and Schmaman[56] in South Africa isolated Salmonella at autopsy in 9 out of 22 fatal cases of gastro-enteritis in Bantu children. Salmonella is spread by contact with patients or symptomfree carriers. The importance of animal, bird and reptile carriers and contaminated animal feeding stuffs containing animal or fish protein was recently stressed again by Taylor.[8] The size of the infecting dose influences the production of clinical disease.[57]

Hodes[58] gave a review of the entero-pathogenic E.coli in relation to infantile gastro-enteritis pointing out the importance of the organism in epidemics in newborn nurseries. Thomson et al[59] also pointed out that with few exceptions most of the literature on gastro-enteritis associated with E.coli deals with hospital outbreaks in infants under 1 year old. In their investigation the illness was mild and most of the infected babies were free of symptoms. These aspects had also been demonstrated by Taylor[8,60] and Giles etal.[6] The organisms are believed to be fairly host specific and neither animals nor foods play an important role in their spread. Clinical cases and child carriers are the main sources.[8] A relationship between the number of organisms excreted and the clinical severity of the illness has been claimed by a worker from the U.S.S.R. in a report to the World Health Organistion.[61]

Reports on gastro-enteritis in the population do not always mention E.coli but when mentioned the incidence is usually low.[3,26] In South Africa Coetzee and Pretorius[62] failed to show a significant difference in incidence of E.coli between kwashiorkor patients with diarrhoea (20%) and control subjects (17%). In 1958 Smythe and Naude[63] isolated specific E.coli in 9 out of 75 patients with gastro-enteritis admitted to a hospital in Cape Town. Shigella therefore seem to be the most common single pathogen in diarrhoea outbreaks in the community. E.coli has the highest incidence in institutions particularly in the neonatal period and does not always produce symptoms.

A variety of Entero-viruses have been shown to be associated with diarrhoea.[64] Here again the importance in nurseries and institutions has been stressed.[58] From available information it was suggested that the clinical illness is mild, of short duration and unimportant as a cause of death in either babies or adults.[8] E.C.H.O. viruses have been demonstrated in outbreaks of diarrhoea in U.S.A.[65,66] although their pathogenicity has not been proved beyond doubt. Silent infections with entero-viruses have been shown in Bantu children around Johannesburg[67] but in a recent study on gastro-enteritis the results were inconclusive regarding a virus aetiology of the diarrhoea.[68]

The common occurrence, particularly of Ascaris has often been shown in malnourished children with diarrhoea.[38,69,70,71.] Interferance with nitrogen metabolism of the host was demonstrated[72] and Jelliffe[16] indicated the additional nutritional hazard of heavy infestation to malnourished children. It is however, not universally accepted that diarrhoea is produced by Ascaris and no way exists of measuring the morbidity produced by them.[73]

Giardia lamblia is an accepted pathogen producing malabsorption states and diarrhoea.[74,75.]

The evidence of interference with absorption is convincingly demonstrated for both Ascaris and Giardia. A causal relationship to diarrhoea is more controversial and less easily demonstrated. It is interesting to note the common occurrence of parasites in malnourished children, often present in large numbers and multiple in kind.[70] There is evidence to suggest that such heavy and multiple infestations are unlikely if not impossible in a wellnourished host.[7

The role of parenteral infection is a difficult aspect to evaluate. Parenteral diarrhoea has been said to be " undoubtedly an overrated clinical concept"[3] Gordon[77] thought it unimportant in wellnourished children but "perhaps still valid in the acute diarrhoea of malnourished young children". Taylor[8] stressed the host-parasite relationship as an important factor in the production of clinical disease. In a paper with Carter[60] she demonstrated the absence of diarrhoea in a nursery with certain strains of E.coli or with acute coryza. Yet the children who had both E.coli and coryza showed symptoms of diarrhoea.

Kahn[20] indicated that the majority of his patients with mild diarrhoea in winter had respiratory tract infections. Respiratory disease is probably the most commonly occurring disease in winter but diarrhoea also occurrs frequently in the same localities in winter. A causal relationship would be much more convincing if one could show that the majority of children with respiratory tract infections presented with diarrhoea. The fact that many of the children with diarrhoea had respiratory infections does not convey the same implication. It is true to say that the majority of children with Shigella infections have diarrhoea. If then, Shigella is found in a study of diarrhoeal disease one can accept a causal relationship without really proving it in every case.

An important aspect in the production of diarrhoea is the relation of the disease to breast feeding. Gordon[77] recently stated that "the diarrhoeas and dysenteries of early life in underdeveloped countries are so intimately related to weaning as to constitute an epidemiological entity". Many reports on gastro-enteritis stress the fact that very few of the children are fully breast fed at the time when they present with their diarrhoea and the morbidity and mortality are higher in the artificially fed children.[10,16,24,25,78,79,80]

Today advanced nations do not have a problem with diarrhoea even when artificial feeding is almost universally practised.[2,31] However, Davis[79] and Levy[80] both wrote about the difficulties encountered with artificial feeding in poor socio-economic environments in America in 1912. Davis[79] related the vast differences in infantile mortality between New Zealand and Australia and Boston to the high rate of bottle feeding in the latter. Levy[80] from New York said that bottle fed babies were 10 times as likely to die from gastro-enteritis as the breast fed infants. He pointed out that specific instruction to mothers reduced the mortality rate even if they received nothing but advice and encouragement. The most important advantage of breast feeding is probably the reduced exposure to infectious agents[3] and the fact that infants are mostly adequately nourished while on the breast. The satisfactory growth of such children has been stressed by several workers. Growth failure sets in after weaning[81,82,83,84] and morbidity and mortality from gastro-enteritis increase greatly.[16]

One or more of the above organisms are considered to initiate the majority of attacks of diarrhoea. Diarrhoea is less frequently accepted as a sign of malnutrition. However, a variety of abnormalities which are present in states of malnutrition could be responsible for the diarrhoea in the absence of infection. In general, deficiency states tend to be multiple[85,86] and a combination of abnormalities may operate in the same patient. It is not clear

whether these structural and functional changes would produce diarrhoea in pure uncomplicated states of malnutrition or whether an additional "trigger mechanism" is needed to initiate the attack which is then perpetuated because of the malnutrition. Recent work on experimental kwashiorkor in Rhesus monkeys has already provided useful information on certain aspects of pure protein-calorie malnutrition.[87] Such work could with great benefit be extended and more widely studied.

The small intestinal mucosa has a very rapid turnover of protein.[88,89] It is easy to understand that protein deficiency should have a marked effect upon its function. In kwashiorkor gross atrophy of the small bowel mucous membrane has been demonstrated.[90,91] In experimental kwashiorkor in Rhesus monkeys, profound changes of the gastro-intestinal tract have been demonstrated. These included changes in the brush border of the small bowel mucosa.[87] It is not clear whether such changes occur early or only when depletion is advanced.

Pancreatic atrophy and deficiency of pancreatic enzymes have often been described in kwashiorkor and marasmus.[85,90,92,93,94,95] These are associated with diarrhoea and malabsorption of nutrients. The complete absence of pancreatic enzymes can precede clinical signs of kwashiorkor.[94,96] On recovery pancreatic function may return to normal very rapidly.[85]

Inhibition of pancreatic enzymes have been demonstrated in infections unassociated with malnutrition[97] and also in diarrhoeal disease.[98] Existing abnormalities in malnutrition could therefore be aggrevated by infection. Dean[99] and more recently Bowie et al[100] described diarrhoea in relation to lactose intolerance in patients with advanced protein-calorie malnutrition. The diarrhoea was dramatically controlled with a lactose-free diet, even in the presence of infection.[100] It has not yet been established whether diarrhoea is a result of

enzyme deficiencies or of structural mucosal changes alone. A congenital metabolic defect is unlikely since the lactose intolerance was reversible on recovery from malnutrition. Bowie[101] found that all his patients with infection had intolerance to lactose while only one third of the patients without infection had a similar dysfunction. He therefore speculated that infection may be an important aggrevating factor. Smythe[102] found a rapid response of diarrhoea in kwashiorkor patients to treatment with a combination of broadspectrum antibiotics and nystatin, holding the view that infection was the main factor determining the prognosis. However, objective data on stool weights and a proper control series were absent in his study. It is possible that the almost complete sterilsation of the bowel was responsible for the control of the diarrhoea, as opposed to the control of infection, by preventing the fermentation of the unabsorbed disaccharides. Further work along these lines may elucidate the problem.

The common occurrence of iron deficiency anaemia among the non-White child population of Cape Town has been stressed by Lanzkowsky.[105a] Abnormalities of the gastro-intestinal tract related to diarrhoea have been demonstrated in states of iron deficiency anaemia.[103,104] These findings include various degrees of atrophy and inflammation of the gastric and duodenal mucosa and malbasorption of nutrients which were reversible with iron therapy. Impairment of gastric acid secretion has been demonstrated in relation to iron deficiency anaemia[104,105b,106] and malnutrition[107,108] often associated with chronic gastro-enteritis.[105b] Waterlow[109] was unable to confirm impaired acid secretion in patients with kwashiorkor. In the studies of malnourished patients the findings were not analysed in relation to the presence or absence of anaemia, which is an important omission. Achlorhydria has been suggested as a factor in the production of diarrhoea[20] and improvement of diarrhoea was described after

treatment with hydrochloric acid.[110] Acid secretion improved almost invariably after correction of the anaemia[104,105b] suggesting that achlorhydria is a result of the anaemia and not a cause. In the studies on acid secretion a variety of test meals were used[105b,109] and patients often had a combination of diarrhoea, anaemia, malnutrition and infection. It is therefore not always possible to evaluate cause and effect. Naiman et al[104] stated that impaired acid secretion in their study was not related to low weight for age and their patients did not have infections. The relation to anaemia was thus well demonstrated.

The gastro-intestinal effects of vitamin deficiency states have been reviewed by Jelliffe[16] who indicated again the common occurrence of diarrhoea in relation to such deficiencies. It is probably not a major cause of epedemic or endemic diarrhoea although such situations do arise.[61,111]

It is furthermore important to stress that structural and functional changes are not limited to the gastro-intestinal tract in states of nutritional deficiency. The importance of such changes in relation to diarrhoea have often been stressed.[112,113.a-c]

The above data clearly demonstrate the gross and widespread changes associated with nutritional deficiency. Considering these it is surprising that metabolic function is not more grossly abnormal and that so many aspects of metabolism are seemingly normal in the face of severe depletion.[112.]

## A SUMMARY OF THE MAIN FEATURES OF THE DISEASE.

The disease is mainly concentrated in the underdeveloped countries and in those undergoing rapid industrialisation. Gastro-enteritis is recognised as a major cause of death during the rapidly growing periods of infancy and early childhood and comprises a considerable medical and public health problem in many

countries of the world.

The incidence and characteristics of the disease differ significantly between malnourished children and those who are wellnourished. In the former it tends to be prolonged and frequently recurrent and shows a lack of spontaneous recovery. In well-nourished children the disease is acute, of short duration and complete recovery is the rule.

The aetiology of the disease is varied and often obscure. Enteral infection is considered the most frequent precipitating cause of an acute attack of diarrhoea. The frequent association with malnutrition and poor socio-economic circumstances has been pointed out and the relation of the first attack to the introduction of bottle feeding stressed.

The main characteristics of the home environment are fairly constant in malnourished groups with diarrhoea. Poverty, ignorance, poor hygiene and lack of suitable foods are interwoven. The pattern varies in the relative significance of these factors in a particular patient, population group or geographic locality.

Evidence of preceding malnutrition in patients with diarrhoea and the influence of malnutrition on the prognosis has been pointed out by several workers

Infection and parasite infestation influence the nutritional status and often this is further aggravated by the common practise of prolonged starvation when diarrhoea is present. These factors are responsible for the acute nutritional breakdown of previously malnourished patients rather than being the major cause of chronic malnutrition.

The evidence indicating that diarrhoea could be a sign of nutritional deficiency is reviewed. Structural and functional changes are numerous and many of these are concentrated on the gastro-intestinal tract.

The literature on the subject of gastro-enteritis is vast and often confusing. Many aspects of the disease have not been adequately investigated.

The multiplicity of associated factors often complicate adequate assessment and evaluation of available data.

Basically the disease is preventable. The urgent need for large scale programmes of prevention centred mainly upon the infants and young children is obvious.

## A SUMMARY OF THE PROBLEM OF GASTRO-ENTERITIS IN SOUTH AFRICA AND IN CAPE TOWN IN PARTICULAR.

Working in a children's hospital in Cape Town for some years, an increasing awareness of the magnitude of this problem among the non-European infants and children has been inescapable.

The importance of the relationship of malnutrition and infection has been repeatedly stressed in different ways by the senior staff who have also indicated the need for more data concerning the disease as it is seen in and around Cape Town.

In 1949 Brock[9] pointed out that great differences in vital statistics between European and Cape Coloured people existed mainly in relation to the "social diseases" such as infantile gastro-enteritis. Since then there have been several publications from Cape Town on gastro-enteritis.[10,18,21,29,30] All the workers indicated the high mortality and morbidity rates in relation to malnutrition. Robertson et al[10] and Truswell[21,29] stressed the differences between the racial groups. They showed the similarity of the European population figures to those of the industrially developed countries and of the non-European figures to those of the underdeveloped countries of the world. Gastro-enteritis in the non-European children was strongly associated with malnutrition and poor socio-economic circumstances. None of these papers included an analysis of the incidence of infection.

Kahn[20] from Johannesburg indicated a similar situation to that in Cape Town. The majority of his patients were Bantu. He did investigate infection and pointed out the seasonal differences of both infection and disease incidence. The disease has a peak incidence in summer but large numbers of cases occur throughout the year.

Recent figures[10,11] indicate that diarrhoea mortality is still high in the Republic especially in the age group under 5 years. In certain areas there has been a steady decline in mortality rates in recent years.[12,22.] In the Cape Town municipal area deaths are steadily dropping[12] but outside the municipal area mortality remains high. At one children's hospital outpatient department alone, there were 314 deaths from gastro-enteritis during the 18 months from January 1963 - June 1964.[19] This does not include the inpatient deaths. During this time more than 6,000 patients received intravenous fluid therapy in the resuscitation room at the outpatient department. If 50% of these patients were underweight and had hypo-albuminaemia[21] it means that there were at least 3,000 children in a state of "pre-kwashiorkor" in this department alone during 18 months. At this hospital the outpatient numbers are increasing every year and there is no indication that diarrhoea incidence is dropping.

The following table gives an indication of the situation in 1960. These figures were compiled from the records of cases examined during the study reported by Ford et al.[18.] The total number of patients seen during March and July are given in addition to the number in whom gastro-enteritis was the primary diagnosis.

The weather in March is still hot and in July it is wet and cold.

Incidence of Gastro-enteritis in March and July 1960

O.P.D. 1960 INCIDENCE OF GASTRO-ENTERITIS.

| Non-European. March & July. | Less than 65% Expt.Wt. | 65-80% Expt. Wt. | More than 80% Expt.Wt. |
|---|---|---|---|
| Total No. of Patients | 325 | 1009 | 1179 |
| No. with G.E. | 151 (46%) | 274 (27%) | 121 (10%) |
| **March.** | | | |
| Total No. of Patients | 191 | 622 | 553 |
| No. with G.E. | 113 (59%) | 235 (38%) | 88 (16%) |
| **July.** | | | |
| Total No. of Patients. | 134 | 387 | 626 |
| No. with G.E. | 38 (28%) | 28 (7%) | 33 (5%) |
| **European. March & July.** | | | |
| Total No. of Patients. | 8 | 28 | 252 |
| No. with G.E. | 2 | 1 | 9 (4%) |

There were 54% of all non-European and 12% of European patients below the 3rd percentile in weight. Of the non-European patients with gastro-enteritis 75% were below the 3rd percentile. Weights above the 50th percentile occurred in 58% of European patients and 12% of non-European patients.

In March 32% of all non-European patients had gastro-enteritis and in July only 9% had gastro-enteritis. During the two months only 4% of the European patients had gastro-enteritis. The incidence of the disease was very much lower in the patients who were within the normal range of weight for age than in the low weight patients. In Winter the incidence remained high only in those who were grossly underweight.

These figures are in keeping with reported series. They show the strong association of gastro-enteritis with malnutrition. The difference in incidence between European and non-European children is by no means as great in the normal weight children as it is in the low weight group.

## DESIGN AND PURPOSE OF THE PROJECT.

This work was undertaken in an attempt to define more clearly some of the factors involved in the syndrome of gastro-enteritis as it is seen at a children's hospital where the bulk of the work in Summer and a considerable proportion of it in Winter revolves around diarrhoeal disease in infants and young children of the non-European community.

Cape Town offers many advantages to this type of study.

(a) There is almost no limit to the amount of clinical material.

(b) Tropical diseases which often influence the disease in other parts do not occur here.

(c) With the excellent facilities available, follow-up studies are easy.

(d) The population is representative of a rapidly developing industrial community and findings could be applied to similar situations elsewhere.

This study was planned with the following objects in mind.

I. Nutritional status: An attempt was made to determine the role of malnutrition in the epidemiology of gastro-enteritis. It was decided to try and define low weight as an entity in terms of accepted normal standards for wellnourished children. Kwashiorkor and marasmus are well known clinical entities and easily recognised. They represent only the most advanced stages of protein-calorie malnutrition. The majority of children with lesser degrees of deficiency do not present such obvious clinical signs and may show only growth failure.[114] An easy way of recognising this failure would obviously enhance early diagnosis. It would also be useful in studies to estimate the full extent of such a deficiency with the view to public health planning and prevention programmes.

2. The role of infection: There is a considerable lack of reported data on the incidence and type of infection in gastro-enteritis in Cape Town. In general, a great deal of controversy exists on the role of infection in diarrhoeal disease and of its importance relative to malnutrition and other aspects of the disease. Reports often deal either with infection or with malnutrition and very few comprehensive studies including both aspects have been undertaken in this country. In this study it was planned to evaluate the inter-relationship of infection and malnutrition in gastro-enteritis.

3. Gastric function: Achlorhydria has been mentioned among the varied causes of diarrhoea in malnourished and anaemic children. It was therefore decided to test gastric acid secretion in kwashiorkor, as representative of the most severe form of malnutrition and therefore likely to show the highest incidence of associated abnormalities. This part of the study also provided an opportunity to evaluate the use of the Augmented histamine test[115] in the study of gastric function in young children. The use of this test, at the time of this study had not been reported in small children or in kwashiorkor.

4. Treatment: (a) Agreement has not yet been reached on the routine use of antibiotic drugs in the treatment of gastro-enteritis and preference in the choice of drugs varies greatly. Supportive therapy has been fairly well standardised in Cape Town.[30] Although this experiment was not primarily designed as a therapeutic trial, it was decided to compare the value of two commonly used drug régimes in gastro-enteritis within the experimental design.

(b) In the outpatient department it is the impression of many doctors that a certain number of children have continuous or frequently recurrent episodes of diarrhoea which do not respond to régimes of treatment with a variety of antibiotics. Often no adequate cause can be found. The mothers frequently

complain that diarrhoea is related to milk feeding and reconstituted dried skimmed milk is commonly blamed. In the light of recent evidence of lactose intolerance in malnourished children[100] it was decided to test the therapeutic value of a lactose-free formula in children with severe gastro-enteritis.

5. Socio-economic circumstances: Much information is available on this factor in relation to diarrhoea and malnutrition. It was, however, decided to include a detailed analysis of the social and economic environment of the patients studied in order to cover as many aspects of the associated features of the disease as possible.

6. Follow-up: No long term follow-up has yet been undertaken on a group of patients with gastro-enteritis in this town. This was considered a good opportunity to obtain information on morbidity and subsequent growth in a group of patients with whom the investigator had become well acquainted.

## CHAPTER 2.

### Material and Methods.

1. Clinical
   (a) Gastro-enteritis study in the out-patient department.
   (b) Control study in growth failure and nutritional status in patients without diarrhoea.
   (c) Gastric acid secretion in kwashiorkor.
   (d) Lactose-free diet trial.

2. Laboratory methods.

# MATERIAL AND METHODS.

## CLINICAL MATERIAL AND METHODS OF INVESTIGATION.

### 1. Gastro-enteritis study in the out-patient department.

This study was done on a group of children with dehydrating gastro-enteritis who attended for treatment at the out-patient department of the Red Cross War Memorial Children's Hospital. The study was undertaken in two parts. Trial I. was conducted between March and June 1962 (autumn and early winter). Trial II. was conducted between November 1962 and February 1963 (summer).

The trials consisted of 50 and 51 non-White children respectively.

The criteria for selection of cases and the methods of investigation were identical in the two trials.

Patients were selected according to the following criteria:-

1. Diarrhoea as the presenting complaint.
2. The presence of clinically detectable dehydration.

They were excluded if they (1) Had received intravenous fluid therapy on any occasion during the previous month.

(2) Showed clinical signs of kwashiorkor e.g. oedema or typical skin lesions.

(3) Had gross underlying illness e.g. parenteral infection, tuberculosis or other defects.

(4) Were moribund or too ill to warrant investigation.

The first two patients fulfilling the above criteria that were admitted to the resuscitation room in the out-patient department each week-day before noon, were taken into the series. Beds were reserved for these cases for the duration of each study period.

## CLINICAL INVESTIGATIONS.

A. Medical: A detailed medical history was taken and a full clinical examination carried out personally by the investigator in every case.

All data were recorded on specially prepared forms.

Each child was weighed on 3 occasions:-

1. On admission - before any treatment was given.
2. After completion of intravenous fluid therapy.
3. Twenty-four hours after fluid therapy had been completed.

The following samples were obtained for analysis:-

I. Blood: Blood was taken by venipuncture usually from an external jugular vein. If this failed one attempt was made at an internal jugular vein puncture and failing this the procedure was abandoned. Blood was taken for the estimation of serum proteins, haemoglobin, P.C.V. and culture.

Three blood samples were taken from each patient.

1. Before the intravenous fluid administration was started.
2. Within an hour of completion of the intravenous fluid therapy.
3. Twenty-four hours after fluid therapy had been completed.

In the second trial some of the blood from the first sample was sent for culture.

2. Stool: A fresh sample of stool was collected for microscopy and culture from every case before any treatment was given and repeated on the 3rd day.

The sample was collected into a sterile test tube through a small sterile glass tube specially prepared for the purpose. Ample material is usually obtained by inserting the end of the glass tube into the anal canal to a depth of about i inch. (This method was introduced by Dr. McKenzie, the senior pathologist, for routine use in this hospital in preferance to swabs or the more

commonly used rubber tubing).

3. An X-ray of the wrists and chest was taken of each patient.

B. Social Study:- The mother was interviewed by the Social Worker while the child was receiving resuscitation therapy. The mother stayed with the child in the out-patient department until the completion of therapy, usually 24 hours. She and the patient were then taken home by the Social Worker who utilised the opportunity to inspect the home and environment. The same Social Worker investigated all the patients.

C. Management:

I. Resuscitation: Supportive therapy was the same for all cases.

Fluid and electrolyte replacement therapy was given intravenously through a scalp vein infusion. The amount of fluid, maintenance plus replacement, was calculated according to the estimated degree of dehydration, the age and body weight of the patient.[30].

Sodium lactate of 1/6th molar concentration was given at 10 ml/pound body weight and the balance was given as ½ concentrated Darrow's solution with 2½% dextrose, over a period of 24 hours. Some of this was allowed by mouth to comfort the child (and mother).

2. Feeds: No milk was given during the first 24 hours. After this feeds of reconstituted dried skimmed milk (2½ oz.per pound per day) were begun, or babies were put back on the breast where feasible.

3. Drug therapy: Two regimes of therapy were used. Selection was strictly on an alternate case basis and had nothing to do with clinical condition or history.

I. One intramuscular injection of "Bicillin" 300,000 units and oral Sulphadiazine suspension at 1½-2 grains/lb.body weight per day in 4 divided doses. The Sulphadiazine was given for a period of 5 days.

II. Chloromycetin palmitate 40 mg./lb.body weight per day in 4 divided doses was given for a period of 5 days.

Treatment for worms or Giardiasis was instituted after 5 days or at times even later.

4. Criteria for a change of treatment:

I. If after 24 hours the patient was still dehydrated, intravenous therapy was continued but oral feeding with milk was started as scheduled above.

2. If the patient did not improve according to expectation or if the condition deteriorated, therapy was reconsidered. The therapeutic result was recorded as a failure if drugs had to be changed.

D. Follow-up Study: After the first 24 hours in the resuscitation room all patients were asked to visit the hospital again the next day for a re-assessment of the clinical condition.

Another hospital visit was requested on the 5th day, then again at about 2 weeks, 3 months and one year as a routine. For individual cases hospital visits were not limited in any way.

Home visits were carried out at roughly 3 monthly intervals for 1 year after the first attendance.

Follow-up Investigation:

I. At each visit a superficial clinical examination was carried out and if necessary the patient was referred for treatment to the hospital or clinic.

2. Body weight was recorded at each visit. At the hospital weights were done in the nude but at home children were sometimes weighed with light clothing.

3. A history of illness was recorded and clinic records were studied at each visit.

4. At the final hospital visit after one year a full physical examination was

done and all patients were weighed. In the second trial group, two additional investigations were done:-

(a) The standing height of bigger children and the crown-to-heel length of smaller children were recorded.

(b) A blood sample was taken of each case for serum protein estimation.

E. Control Subjects: Concurrently with each trial a group of control children were studied. There were 11 controls in the first trial and 32 in the second.

These were healthy non-White children without diarrhoea who visited the surgical out-patient department with minor surgical conditions. Alternatively they were examined at the time of a routine visit to the municipal child welfare centres in the areas from which the patients were drawn.

The following procedure was adopted:-

(a) Body weight and age were recorded.

(b) One blood sample was taken for serum proteins and haemoglobin and P.C.V.

(c) One fresh stool sample was obtained for microscopy and culture.

The social study was not done on these children and no follow-up was undertaken.

II. A control study on growth failure and nutritional status in patients without diarrhoea.

This consisted of two parts and was done during 1963-64.

A. Weight, height and serum albumin.

For these investigations a total number of 218 children were studied. They were selected at a number of municipal and welfare day nurseries in Cape Town and at home visits to families.

The following were the criteria for admission to the series.

I. All children were of the non-White racial group.

2. They were symptomfree and had no apparent illness and no history of recent diarrhoea.
3. They had not had kwashiorkor in the past.
4. The age was accurately known.

Investigations:

I. Body weight was recorded for every child. The weights were not always done with the same scale. Patients were not always completely stripped before weighing.
2. A measurement of the height was recorded. The standing height of bigger children and the crown-to-heel length of smaller children were recorded.
3. A blood sample was taken from the external jugular vein in 97 of these children Blood was taken from a selected group to include 43 low weight for age children and 54 weights within the normal percentile range.

B. Kwashiorkor follow-up study:

A group of 50 children were examined 5 years after they had kwashiorkor. They were the first 50 patients who survived for 5 years out of a group of children admitted to a long term follow-up series of kwashiorkor. The person responsible for this follow-up study is Miss Moodie, the research Social Worker of the C.S.I.R. Clinical Nutrition Research Unit at the University of Cape Town.

In addition 34 of their siblings and neighbours who had been followed for 3 years or more were examined. These children are also from a larger group acting as control subjects in the long term kwashiorkor follow-up study.

The following investigations were done on these patients:-

I. Body weight.

2. Standing height.

3. A full physical examination.

4. A blood sample for proteins from the external jugular or arm vein.

5. An X-ray of the chest, wrists and hands.

III. Gastric Acid Secretion in Kwashiorkor.

This study was done on a group of patients with kwashiorkor who were admitted to the Metabolic Research Unit at the Red Cross War Memorial Children's Hospital, Rondebosch, in 1962-1963. The investigation was done in consultation with Dr.I.N.Marks of Groote Schuur Hospital.

Acid Secretion: After a pilot study which served to straighten out many technical difficulties, the tests were performed on 20 kwashiorkor patients.

The diagnosis of kwashiorkor was made on the usual signs of growth failure, hypo-albuminaemia and oedema with or without skin lesions.

All patients were of the male sex. Depending on the clinical condition of the patient the test was done within the first few days of admission. The test was repeated in all cases at a varying interval after initiation of cure according to the following criteria:-

I. A serum albumin concentration above 3 gram%.

2. Loss of oedema and improvement in the general condition of the patient.

The interval varied between 10 days and 3 weeks in the majority of cases.

If achlorhydria was still present, the test was again repeated at intervals, for a period up to 1 year.

Gastric Biopsy: In addition to the study of acid secretion a gastric biopsy was performed on 5 patients. In one patient it was repeated after a year.

Clinical Methods.

Acid secretion was studied by means of the Augmented histamine test as described by Kay in 1953.[115].

After a 12 hour fast, the patient was sedated with intramuscular Paraldehyde. A gastric tube with multiple holes at the distal end was introduced into the stomach through the nose. The position of the tube in the stomach was confirmed by one straight X-ray film of the abdomen.

The fasting juice was suctioned off. Following this basal secretion was collected into a test tube for a period of a ½ hour . The patient was then given an injection of Anthisan in a dose of 3-4 mg/kg.body weight, and a further ½ hour of basal secretion was collected.

Histamine acid phosphate was then injected subcutaneously in a dose of 0.08 mg/kg. body weight, or an equivalent of 8 body weight doses. Thereafter fluid was collected in 4 divided samples for 15 minutes each during the next hour.

Fluid was collected by continuous suction by means of a Stedman pump. A pressure regulating valve was attached to the pump to facilitate mild suction, which was kept to a maximum of 7 cm of mercury.

Gastric Biopsy: Patients were starved for 12 hours and were then sedated with Paraldehyde given as an intramuscular injection. The biopsy was performed with a Rubin multipurpose biopsy tube which was inserted into the stomach through the mouth.

IV. The Diet Trial in Gastro-Enteritis.

This was undertaken in the Metabolic Unit at the Red Cross Hospital during the period November 1963- May 1964.

The investigations were done on 25 non-European male children with dehydrating gastro-enteritis. For practical reasons concerning sample collections, children weighing less than 7 lbs. were not admitted to the series. Other than this the criteria for selection were the same as described for the gastro-enteritis trial.

Clinical Methods.

Examination: A full history was taken and a complete physical examination was done.

Investigations:

I. Body weight was recorded in the nude on admission before any fluid therapy had been given.

2. Crown-to-heel length was recorded on every case.

3. Blood samples were taken from the external jugular vein or an internal jugular vein as previously described, for protein, haemoglobin and P.C.V. estimations.

The following samples were taken:-

(1) Before intravenous fluid therapy had been given.

(2) Within an hour after the completion of the fluid therapy.

(3) Twenty-four hours after fluid therapy had been discontinued.

(4) At 24 hour intervals thereafter for 2 more days.

4. A fresh stool sample was obtained for microscopy and culture, on admission and again after 5 days.

5. Separate 24 hour collections of stool and urine were obtained for the first 5 days in hospital.

Management.

Supportive therapy with intravenous fluids was the same in all cases and was conducted in the same way as described for the gastro-enteritis trials.

All patients were given an additional 1½ gm. of potassium chloride by mouth per day and 0.6 ml. of Abidec daily.

Feeds:

Feeding was started after 24 hours.

Alternate patients were given Cows' milk or a lactose free formula.

Milk feeds were not diluted and all patients were given a fluid intake of 2½ - 3 oz/lb. body weight per day.

The lactose free formula consisted of the following ingredients:-

| | | |
|---|---|---|
| Casilan | : | 40 g. |
| Sunflower oil | : | 25 g. |
| Glucose | : | 30 g. |
| Water | : | 800 ml. |
| Special salt | : | 4 gm to each day's feed. |

The special salt contained Sodium Chloride 2 g., Potassium Chloride 1 g. and Calcium Chloride 1 g.

Drug Therapy: All patients were given the same règime of treatment which was only changed if progress was not satisfactory.

One intramuscular injection of "Bicillin" 300,000 units was given on admission. Each patient was given a Sulphadiazine suspension orally at 1½ - 2 gr./lb. body weight per day in four divided doses for 5 days.

Worms and flagellates were treated after the test period.

Follow-up: The first 11 patients were kept in hospital for 5 days and the subsequent 14 were kept in for 10 days. Subsequently the patients were seen once only at an interval of one week after discharge.

## LABORATORY METHODS.

Blood: Haemoglobin, packed cell volume and serum proteins were done on each blood sample obtained in the gastro-enteritis trials and on the post-kwashiorkor patients and the symptom-free controls.

Haemoglobin: Venous blood 0.02 ml. was pipetted into 5 ml. of 0.04% ammonia in water and the haemoglobin level read by the oxyhaemoglobin method. A Klett-Summerson Colorimeter previously calibrated against standard haemin and cyanmethaemoglobin solutions was used.

Packed cell volume: A heparinised micro-capillary tube was filled with venous blood and sealed at one end with plasticene. It was then spun for 5 minutes at 11,000 r.p.m. in an International Micro-Capillary centrifuge and read.

Blood Cultures: Blood was taken into a Thioglycolate medium in a screw cap bottle and incubated at 37°C for 5 days, being inspected daily. After 5 days sub-cultures from this were done onto blood agar and boiled blood agar plates and incubated overnight. This was only done in the second trial.

Serum Proteins: Serum proteins were measured by a biuret method (Wolfson et al)[116] standardised by the Kjeldahl nitrogen procedure. Serum albumin was separated by the ether centrifugation method (Kingsley)[117] after precipitating the globulin with 27% sodium sulphate at 37°C (Milne).[118]

Method A. For the first gastro-enteritis trial protein of the reference serum was precipitated with TCA for the Kjeldahl analysis. The NPN after precipitating the protein was subtracted from the total nitrogen to determine the total protein of the sample (Harrison).[119]

Method B. In the second gastro-enteritis trial zinc sulphate was used to precipitate the protein of the reference serum and the nitrogen of the precipitate was determined.

Different factors for converting biuret readings into protein were obtained by these two methods. Method B with zinc sulphate precipitation had been used for all the previous work in this laboratory while method A had been used for this particular trial only.

The results for method A were recalculated to bring them into line with method B. This was done for two reasons (I) The number of control subjects in the first trial was considered too small to represent a normal distribution sample. (II) For purposes of comparison of results it was considered advisable to use the same method throughout the study.

The following procedure was adopted to determine a factor for the conversion of method A to method B.

There were 9 control sera and 12 patients' sera available at the time. These had been stored frozen in the interval of 9 months since the original analysis. There was enough serum only to do estimations in duplicate by one method. These samples were thus analysed by method B. In addition a reference serum was analysed by both methods at the same time. A conversion factor was calculated from these results and all the original results by method A were then recalculated, using the factor.

Method C: For the study on the kwashiorkor follow-up patients and the symptom-free low and normal weight children a slightly different procedure for the biuret method[120] was used and the protein of the reference serum in the Kjeldahl procedure was precipitated with tungstic acid.[121].

The results obtained from the trials here mentioned will not be compared with those of the previous methods Aand B.

Bloods were immediately spun and the serum separated from the cells. Serum was kept frozen until the analyses were done. All estimations were done in duplicate.

In the analysis of results only the serum albumin was used. This had been widely accepted as an index of protein nutritional status.[32,122] To minimise the effects of dehydration and overhydration on serum albumin concentration[21,123] the results of the 3rd blood sample wereused in the gastro-enteritis studies.

Stools: Fresh stool samples were treated immediately in the following way:-

Culture: Inoculation of a MacConkey agar and an S.S. agar plate and tetrathionate broth were incubated at 37°C for 24 hours. The tetrathionate culture was then subcultured onto MacConkey and S.S. agar for a further 24 hours. From the plate cultures two non-lactose fermenting colonies were picked off and inoculated into the sugar media for biochemical identification of Salmonella and Shigella. These were typed by slide agglutination against the specific anti-sera available. All stools were treated in this way. For the second trial entero-pathogenic E.coli were also identified by slide agglutination. Two sweeps of mixed lactose fermenting colonies were suspended in saline and tested for agglutination in the polyvalent anti-serum. If agglutination was positive, the single colonies were picked off until a positive polyvalent agglutination was found. This colony was then typed against the specific anti-sera. Rough colonies, confirmed by agglutination in a 1/500 solution of acriflavine, were subcultured on nutrient agar and blood agar and again tested when reverted to the smooth variations. Antibiotic disc sensitivities were tested on Hartleys agar plate cultures.

Direct examination: Two slides of a saline suspension and one slide of an iodine suspension of each stool were examined macroscopically for cellular exudates, ova and flagellates. If large numbers of yeasts were present, then the stool was also cultured in Littmann's medium and the yeasts identified from their sugar

reactions and the formation of Chlameidospores on Cornmeal agar culture. For the first trial stool concentrates from a zinc sulphate flotation method were also examined for worm ova. For the second trial a Gram-stained smear of each stool was examined microscopically. If large numbers of gram positive cocci in clusters were present, the stool was also cultured on mannite agar to identify staphylococci.

Gastric Juice Analysis.

The volume of each sample of fluid was accurately measured in a measuring cylinder.

The pH of each sample was recorded on a Beckman direct reading pH meter.

Acidity of the samples were analysed for "free" and "total" acid by titration with N/10 NaOH to the end points of Töpfers reagent and Phenolphthalein respectively.[115].

The total acid output was then calculated for the fasting juice, the basal fluid of 1 hour and the histamine stimulated secretion of 1 hour, expressed in milli-equivalents of hydrochloric acid per hour.

Lactic acid content of stools.

Lactic acid concentration was determined on 24 hour stool samples collected from the patients in the "gastro-enteritis diet trial". The lactic acid, after precipitation of the protein, was estimated by a colorimetric method described by Barker and Summerson.[124].

Nitrogen Balance.

Nitrogen balance was done during the first four days on oral feeding in the "gastro-enteritis diet trial". The procedure adopted was the same used in this laboratory for previous reported studies.[125].

Histology of Gastric biopsy material.

Histological preparations of biopsy material were made in the routine laboratory at the Red Cross Hospital. Dr.Anstey, senior assistant pathologist, reported on the findings.

X-ray.

X-rays were reported on by the hospital radiologists. Bone ages were estimated from the appearances of wrists and hands according to the atlas of Greulich and Pyle.[126] The radiologist did not know the clinical condition of the patient but the chronological age was provided on the request forms.

Weight and height analysis.

Normal standard: The Boston percentile charts[127] for weight and height were used as representing the normal expected range. For illustrations of weight distribution all weights were plotted against the Boston percentile chart for boys. Weight charts compiled for normal Coloured children in Cape Town show a lower range than the American especially after the age of 6 months.[128.] (This will be demonstrated in the results section).

Correction for dehydration: All weights were corrected for dehydration in the patients who were dehydrated on admission. In the absence of oedema the best recorded weight after rehydration on day 2 or 3 was used. If oedema was present 11% was added to the dehydrated weight and this calculated weight was used in the assessment of weight for age.[21.]

Degree of low weight.

I. The degree of low weight for age was graded according to the standard suggested by Gomez.[36.] The Boston 50th percentile was used as the theoretical mean ideal weight for age. The weight of the patient was expressed as a percentage of this mean.

The percentage was calculated separately for boys and girls and the grading was as follow:-

| | |
|---|---|
| Normal. | Above 90% of Expected weight. |
| 1st Degree Malnutrition | 90 - 76% " " " |
| 2nd " " | 75 - 60% " " " |
| 3rd " " | below 60% " " " |

2. When using only two grades, i.e. normal weight and low weight for age, the Boston 3rd percentile weight was used as the dividing line. This line coincides almost exactly with 80% of the expected weight (see results). For ease of calculation the weight was considered normal at 81% or more and abnormal at 80% and less.

3. The term "weight deficit" is used to indicate a deviation below the mean expected weight.

Height for age: The measurements of patients were analysed in several ways:-

I. Height was plotted on the Boston percentile chart for height and the chart for boys was used in all the graphs.

2. Height was expressed as a percentage of the theoretical mean using the Boston 50th percentile as the mean expected height.

3. The mean height at birth was taken as 21 inches. From this the actual growth in inches was calculated by subtracting 21 inches from the actual height of the patient. The expected growth by subtracting 21 inches from the 50th percentile height at the given age. The percentage growth of the patient was then calculated thus:-

$$\frac{\text{actual growth in inches}}{\text{expected growth in inches}} \times 100 = \text{growth \%.}$$

This was done separately for boys and girls.

4. The normal theoretical expected height/weight ratio was calculated from the weight at the Boston 50th percentile and the corresponding height at the Boston 50th percentile, and plotted as a linear regression line.

The actual height/weight ratio of 2 groups of patients was calculated and a linear regression line plotted for each group as well as plotting the height and weight of each patient to indicate the scatter around the line. The groups of patients were (a) of normal weight.

(b) of a weight below the 3rd percentile.

## CHAPTER 3.

Results.

1. The gastro-enteritis study
   - (a) Weight for age.
   - (b) Serum albumin.
   - (c) Clinical signs of nutritional deficiency.
   - (d) Diarrhoea history in relation to nutritional status.
   - (e) Infection.
   - (f) Socio-economic aspects.
   - (g) Treatment and follow-up.
   - (h) Summary of findings.

2. Control study on growth failure.
   - (a) Hypo-albuminaemia related to weight deficit
   - (b) Weight and height ratios.
   - (c) Growth studies in post-kwashiorkor patients and their siblings.

3. The diet trial.
   - (a) Nutrition, infection and mortality.
   - (b) Response to a lactose-free diet.
   - (c) Nitrogen balance data.

4. Gastric acid secretion in kwashiorkor.
   - (a) Difficulties encountered.
   - (b) Acid secretion.
   - (c) Gastric biopsy.

5. The influence of dehydration on body weight and serum albumin concentration

## RESULTS.

### I. The Two Gastro-enteritis Trials in the Out-patient Department.

The results of the two trials are combined. Few differences were noted between the groups and these will be indicated in the text.

Racial Distribution: In this study no attempt was made to study the relative incidence of the disease between the different ethnic groups, nor were the characteristics of the disease compared between these population groups. The control subjects were Cape Coloured with very few exceptions. The study groups happened to include members of the three non-White racial groups as follows:-

| Race. | Number of patients. |
|---|---|
| Cape Coloured | 68 |
| Asiatic | 13 |
| Bantu | 20 |
| Total | 101 |

Age Distribution: The age distribution of all patients is demonstrated in Figure I and Table I.

Table I.

101 Gastro-enteritis Patients.

Age in months.

| Under 12 | | | Over 12 | | |
|---|---|---|---|---|---|
| 63% | | | 37% | | |
| 2 - 3 | 4 - 6 | 7 - 11 | 12 - 18 | 18 - 24 | > 24 |
| 13% | 23% | 27% | 22% | 13% | 2% |

The majority of patients were younger than one year. Of the patients

FIGURE. 1.

AGE DISTRIBUTION OF 101 GASTRO-ENTERITIS PATIENTS.


FIGURE. 5.

AGE DISTRIBUTION OF CONTROL SUBJECTS.

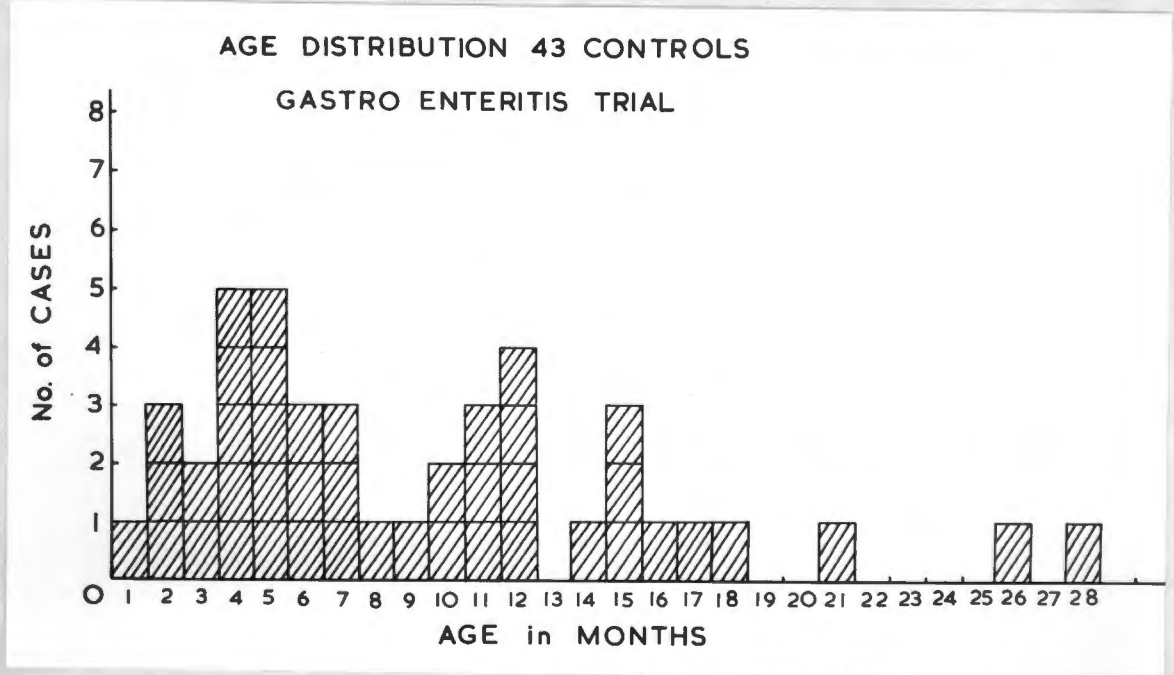


FIGURE. 3.

AGE DISTRIBUTION GASTRO-ENTERITIS SERIES I.

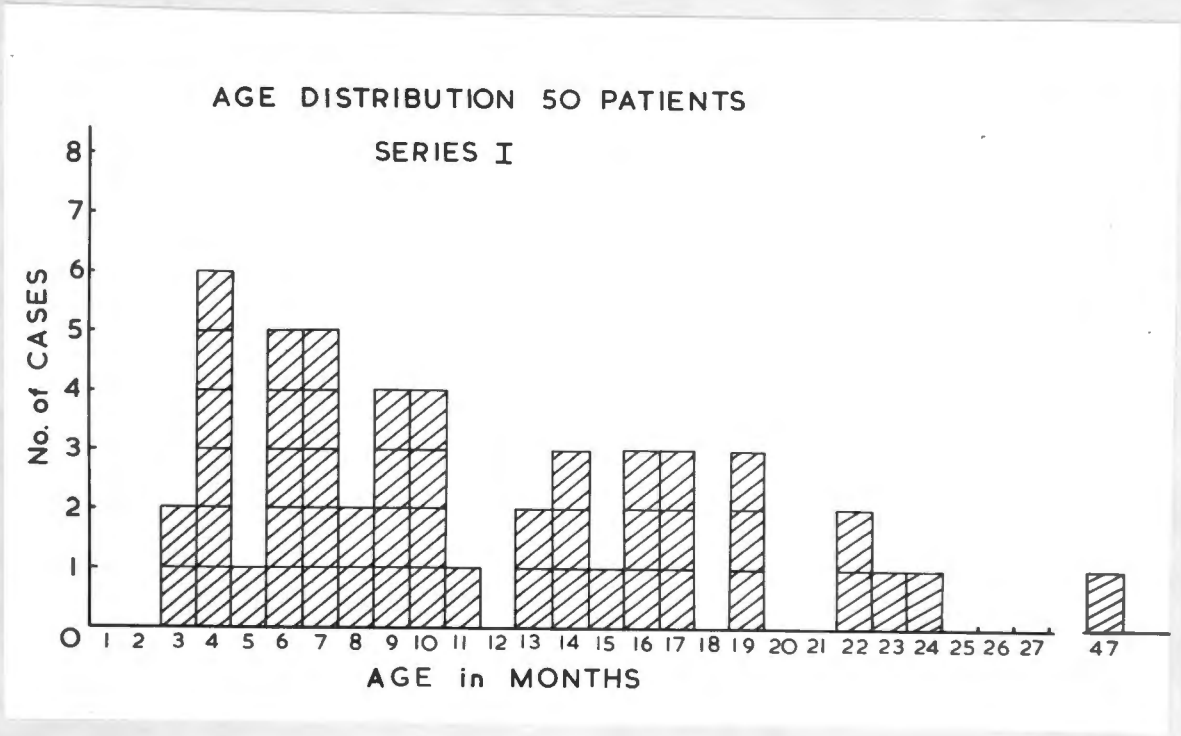



FIGURE.4.

AGE DISTRBUTION GASTRO-ENTERITIS SERIES II.

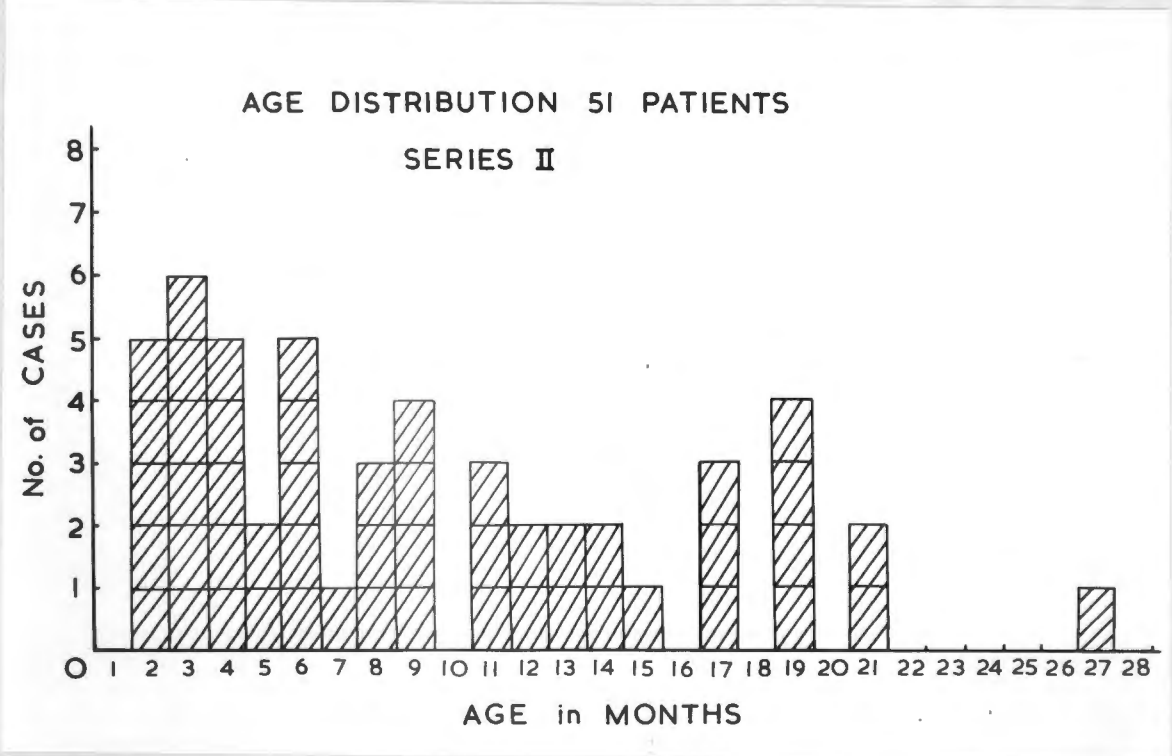


FIGURE. 6.

WEIGHT FOR AGE, BOSTON COMPARED WITH CAPE TOWN RANGE.

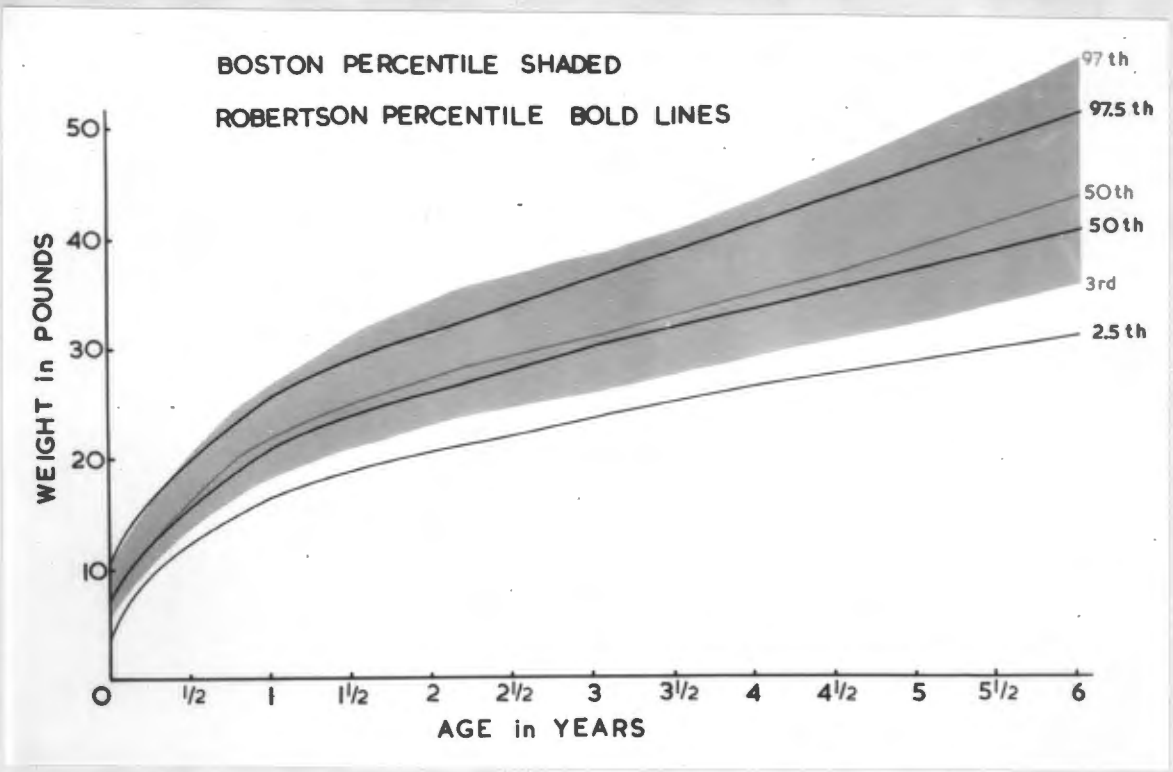
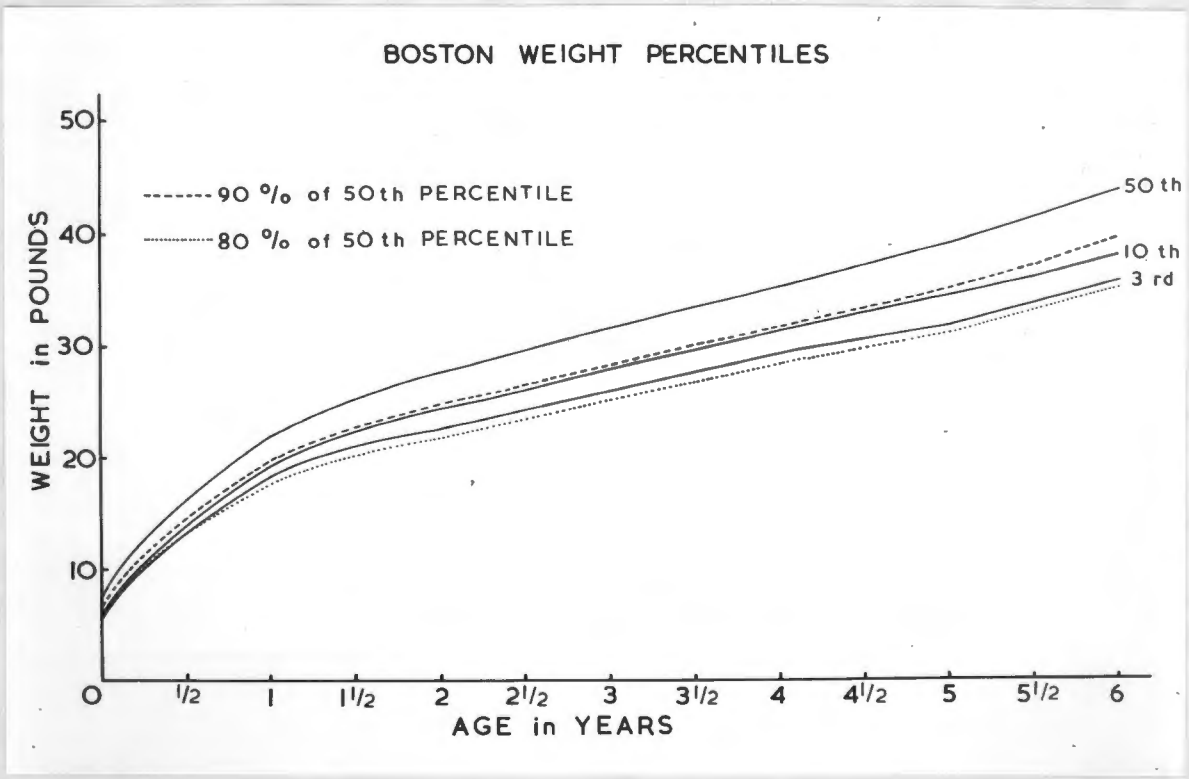



FIGURE. 7.

PERCENT EXPECTED WEIGHT COMPARED WITH PERCENTILE LINES.



under a year old, more than half were younger than 7 months and 20% were under 4 months old. A fair number of cases occurred up to the age of 18 months, but thereafter the incidence dropped sharply. Only 2 patients were over 2 years old.

There were more children under 3 months old in the second trial than in the first. Otherwise the age distribution was similar for the two groups. This can be seen in Figures 3 & 4. The ages of the control subjects matched the cases fairly closely (Fig.5.)

Sex Distribution: There were more male than female patients. The figures are shown in Table 2.

Table 2.

101 Gastro-enteritis Patients.

| | Male. | Female |
|---|---|---|
| All ages | 62% | 38% |
| Under 1 year old | 66% | 34% |
| Over 1 year old | 51% | 49% |

There were more male than female patients. This difference in the sexes was only apparent in the younger patients under 1 year old. Over the age of one year the sexes were equally represented.

Weight for Age: In Fig.6 the difference between the Boston and Cape Town percentile weight distribution is demonstrated. The Boston range[127] is shaded in the background and the Cape Town figures[128] are superimposed. Note how the latter deviate from the Boston figures after the age of ± 6 months.

Figure 7 illustrates the proximity of 90% of expected weight and 80% of expected weight to the 10th and 3rd Boston percentile lines respectively. In the analysis of results "below the 3rd percentile" was used as 80% of expected weight and less.

FIGURE. 8.

WEIGHTS OF PATIENTS COMPARED WITH BOSTON RANGE.

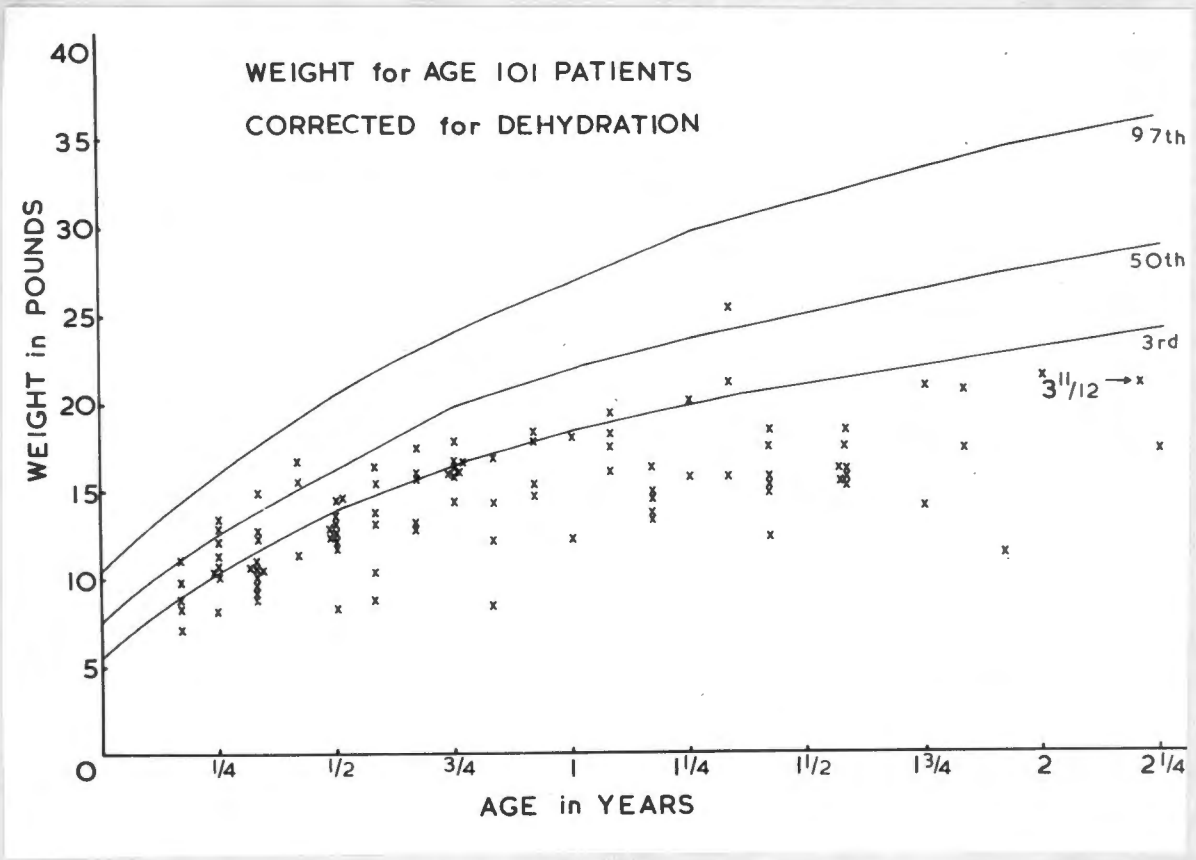
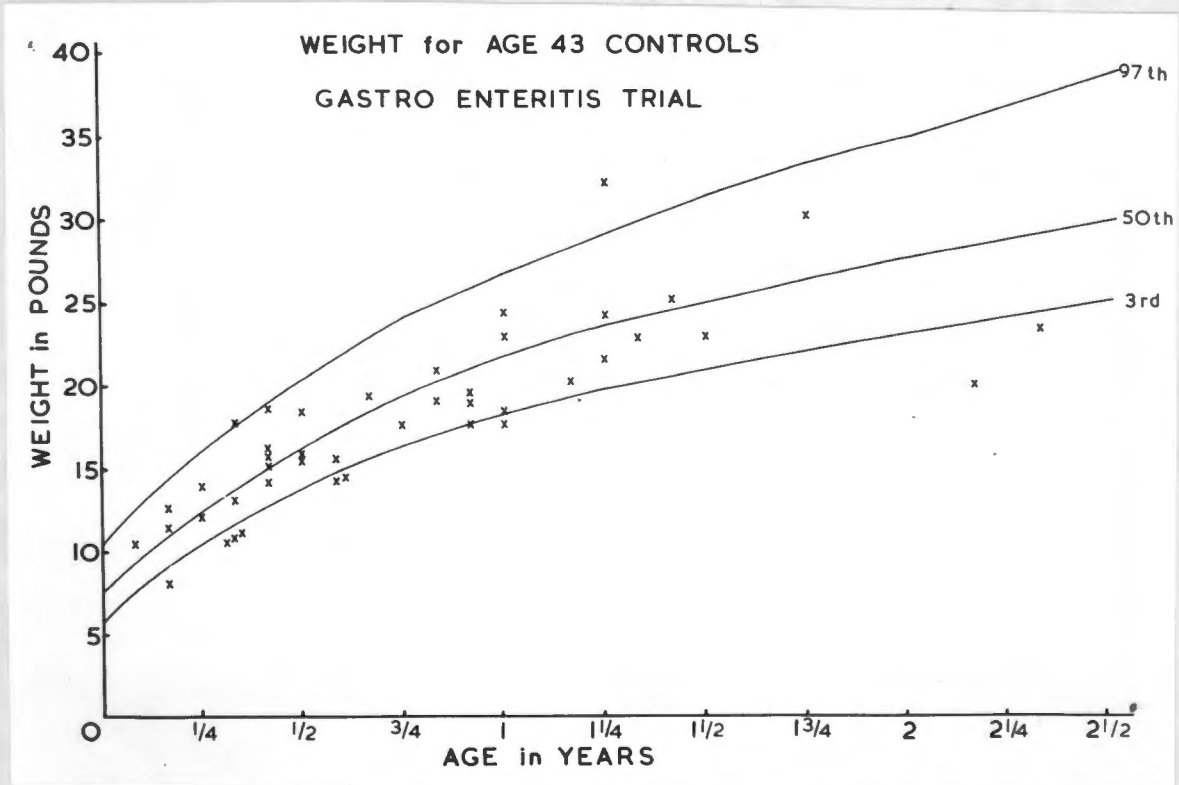



FIGURE.9.

WEIGHTS OF CONTROL SUBJECTS.



"Above the 10th percentile" was used as 90% of expected weight or more.

The corrected weights of the 101 patients are shown in Fig.8. Each patient is represented by a cross against the Boston normal weight range for age. There were 64 patients below normal and 37 patients were within the normal range. Only very few cases were above the mean expected weight. Note how the younger children tend to be normal in weight and the older children are below normal. The deviation from normal is greater with advancing age.

Figure 9 demonstrates the weight distribution of the 43 control subject Here the majority of children are within the normal weight range. This distribution does not represent a random sample of the population because the children were selected from the more privileged sections of the society in general.

In Table 3 the degree of malnutrition by weight is indicated for gastro-enteritis patients and controls.

Table 3.

Degree of Malnutrition by Weight in Patients and Controls.

| Degree of Malnutrition. | Patients | Controls. |
|---|---|---|
| Normal. > 90% expt.wt. | 10.9% | 67% |
| 1st Degree. 90 - 76% | 41.6% | 28% |
| 2nd Degree. 75 - 60% | 37.6% } 47.5% | 5% } 5% |
| 3rd Degree. Below 60% | 9.9% } | 0% } |

Just less than half the patients were 2nd or 3rd degree malnourished and only 11% were above 90% of expected weight for age. The majority of controls were normal.

Low weight for age was more common and more gross in the older children. The number of patients who were below the 3rd percentile weight in each of 4 age groups is shown in Table 4.

FIGURE 10.

LOW WEIGHT INCREASED WITH ADVANCING AGE.

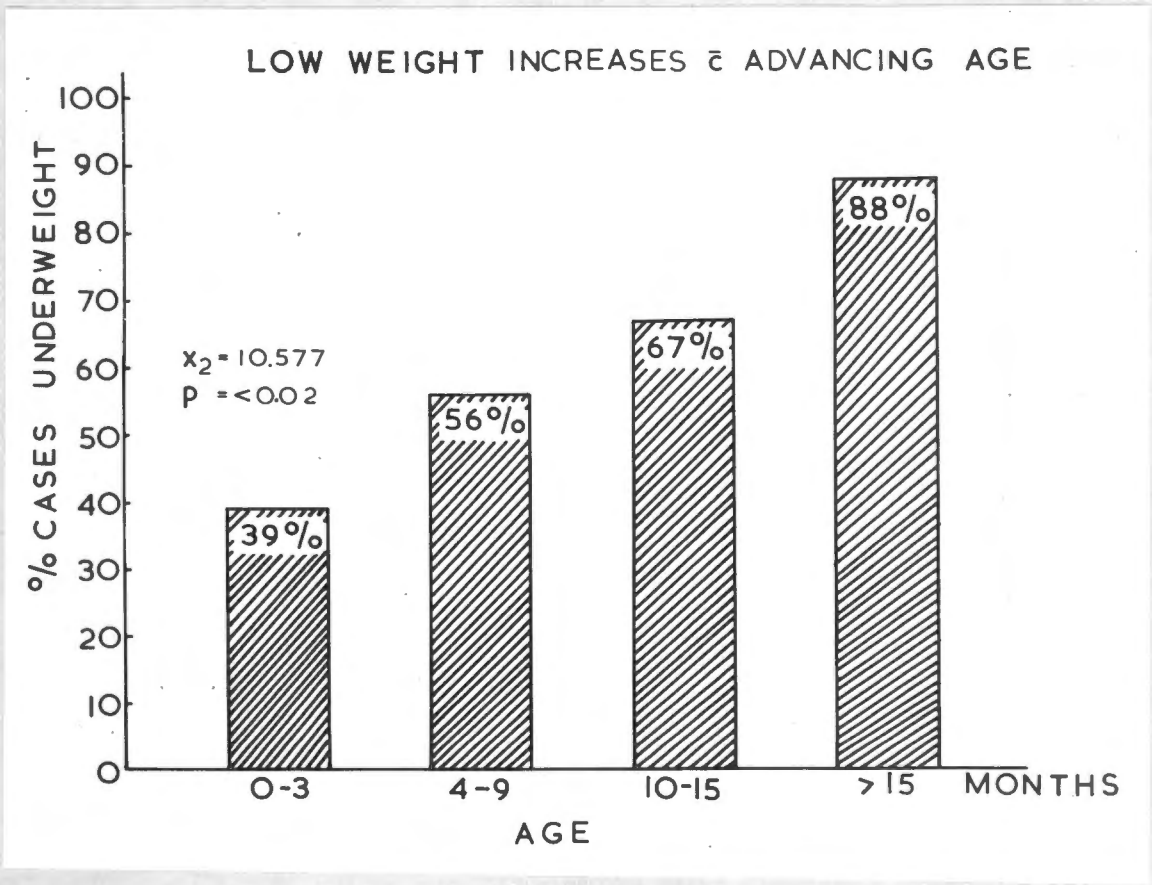


Table 4.

With advancing age significantly more children became underweight for their age.

| | Age in months | | | |
|---|---|---|---|---|
| | 0 - 3 | 4 - 9 | 10-15 | Over 15 |
| Total No. patients. | 13 | 43 | 21 | 24 |
| No. below 3rd percentile | 5 | 24 | 14 | 21 |
| | $x^2 = 10.5767$ | | $p = < 0.02$ | |

Figure 10 demonstrates the significant progressive incidence of low weight with advancing age. The percentage of low weight children are indicated for each of the 4 age groups.

Table 5 indicates the numbers of children in each age group and the number of cases who were 2nd or 3rd degree malnourished in each group.

Table 5.

The degree of weight deficit increases significantly with advancing age.

| | Age in months. | | | |
|---|---|---|---|---|
| | 0 - 3 | 4 - 9 | 10 - 15 | Over 15 |
| Total No. of patients. | 13 | 43 | 21 | 24 |
| 2nd & 3rd degree malnutrition | 3 | 14 | 13 | 18 |
| Mean % expected weight | 85 ± 4 | 80 ± 4 | 71 ± 4 | 69 ± 4 |
| | | p= < 0.30 | p= < 0.01 | p= < 0.005 |

After the age of 9 months the majority of patients were grossly underweight. The progressive weight loss with advancing age is statistically significant. Applying the Student "t" test, the difference between the means of the first group and each of the subsequent groups becomes increasingly more significant.

Conclusion: The majority of patients with severe gastro-enteritis were below the normal weight for their age. Increasingly more of the older children were below the normal weight range and the weight loss was progressively more marked with advancing age.

## SERUM PROTEINS.

### I. Recalculation of method A results:

In Table 6 the results of 9 controls and 12 patients are given as originally done by method A. The results of the same sera repeated by method B are also given and the reference serum done by both methods is included.

Table 6.

Recalculated results of serum albumin in Trial I.

Albumin g%

| Name | Method A | Method B | B/A |
|---|---|---|---|
| J.S. | 4.29 | 4.05 | .94 |
| M.C. | 4.09 | 3.71 | .91 |
| P.S. | 4.49 | 4.00 | .90 |
| P.F. | 4.19 | 4.04 | .96 |
| L.S. | 4.16 | 4.13 | .99 |
| J.R. | 4.45 | 4.07 | .91 |
| E.B. | 4.30 | 4.33 | 1.01 |
| B.M. | 4.70 | 4.21 | .90 |
| P.S. | 4.26 | 3.99 | .94 |
| W.S. | 3.78 | 3.55 | .94 |
| M.M. | 2.95 | 2.88 | .98 |
| A.D. | 2.37 | 2.22 | .94 |
| J.A. | 2.25 | 2.11 | .94 |
| I.P. | 4.31 | 4.14 | .96 |
| D.E. | 3.98 | 4.34 | 1.09 |
| G.B. | 3.40 | 3.36 | .99 |
| D.R. | 2.56 | 2.35 | .92 |
| F.M. | 3.07 | 2.96 | .96 |
| J.C. | 4.28 | 3.98 | .93 |
| E.M. | 3.92 | 3.18 | .81 |
| J.D. | 3.06 | 2.90 | .95 |
| Mean | 3.76 | 3.55 | .94 |
| Reference Total Protein | 6.96 | 6.57 | .94 |

The ratio of B/A was calculated for the individual analyses and for the mean values. The mean ratio of B/A for the repeated results and for the reference serum was 0.94. This was used as the conversion factor and all the original values of Trial I. were multiplied by 0.94 and the results used in the analyses to follow:-

II. Serum albumin in relation to dehydration:

All three blood samples were obtained in 82 patients with gastro-enteritis. The results of these are shown in Table 7 to demonstrate the fluctuation with the state of hydration of the patients. (Less than three samples were obtained from 19 patients and they are not included in this analysis).

Table 7.

Serum albumin in relation to dehydration.

| Blood Sample | Mean. | Range. |
|---|---|---|
| 1. | $4.02 \pm .80$ | 2.31 - 5.60 |
| 2. | $3.02 \pm .53$ | 1.74 - 3.92 |
| 3. | $3.30 \pm .60$ | 1.88 - 4.64 |

While dehydrated (1) the mean serum albumin was significantly higher than immediately after intravenous therapy (2) ( $t = 9.624$ $p < 0.001$).

Blood obtained on the 3rd day (3) showed a significant rise over the previous day ($t = 3.164$ $p < 0.01$) but was still significantly lower than that of the first sample.

This 3rd day sample was considered to give the best reflection of the albumin concentration, and was therefore used to calculate the incidence of hypo-albuminaemia in relation to body weight.

There were 3 low albumin values of the first day. Blood was not obtained from these cases subsequently. These results are included in calculations where merely the incidence of hypo-albuminaemia is concerned.

III. The incidence of hypo-albuminaemia in the patients with gastro-enteritis:

Blood was obtained from 84 patients on the 3rd day and the results are shown in Table 8 together with control values.

Table 8.

Serum albumin in gastro-enteritis and control subjects.

| | Mean. g% | Range. g% |
|---|---|---|
| 84 Patients. | 3.25 ± .61 | 1.88 - 4.64 |
| 42 Controls. | 3.89 ± .26 | 3.28 - 4.42 |
| | t = 6.504 | p = < 0.001 |

All values that were more than 2 standard deviations below the mean of the controls were considered abnormal (3.37 g%).

One of the control subjects had a value lower than this.

Of the 84 patients there were 42 with serum albumin concentrations below 3.37 g% and a further 3 had low values of the first day sample. Hypo-albuminaemia thus occurred in 45 of 87 patients (52%). The mean albumin of the patients was significantly lower than the controls.

III. Hypo-albuminaemia in relation to age and body weight.

Age: Comparing 3 age groups it became clear that hypo-albuminaemia, like low weight, occurred with increasing frequency in the older age groups. In Table 9 the incidence of hypo-albuminaemia (i.e. albumin below 3.37 g%) is shown for each of the 3 age groups.

Table 9.

Hypo-albuminaemia occurred more frequently in the older children.

| | Age in months. 0 - 3 | 4 - 9 | Over 10 |
|---|---|---|---|
| Total No. patients. | 11 | 35 | 41 |
| Low albumin | 3 | 15 | 27 |
| | $x^2$ = 7.019 | p = < 0.05 | |
| Mean albumin | 3.57 ± .52 | 3.44 ± .44 | 3.00 ± .67 |

FIGURE. 11.

**HYPO-ALBUMINAEMIA CORRELATED WITH LOW WEIGHT FOR AGE.**

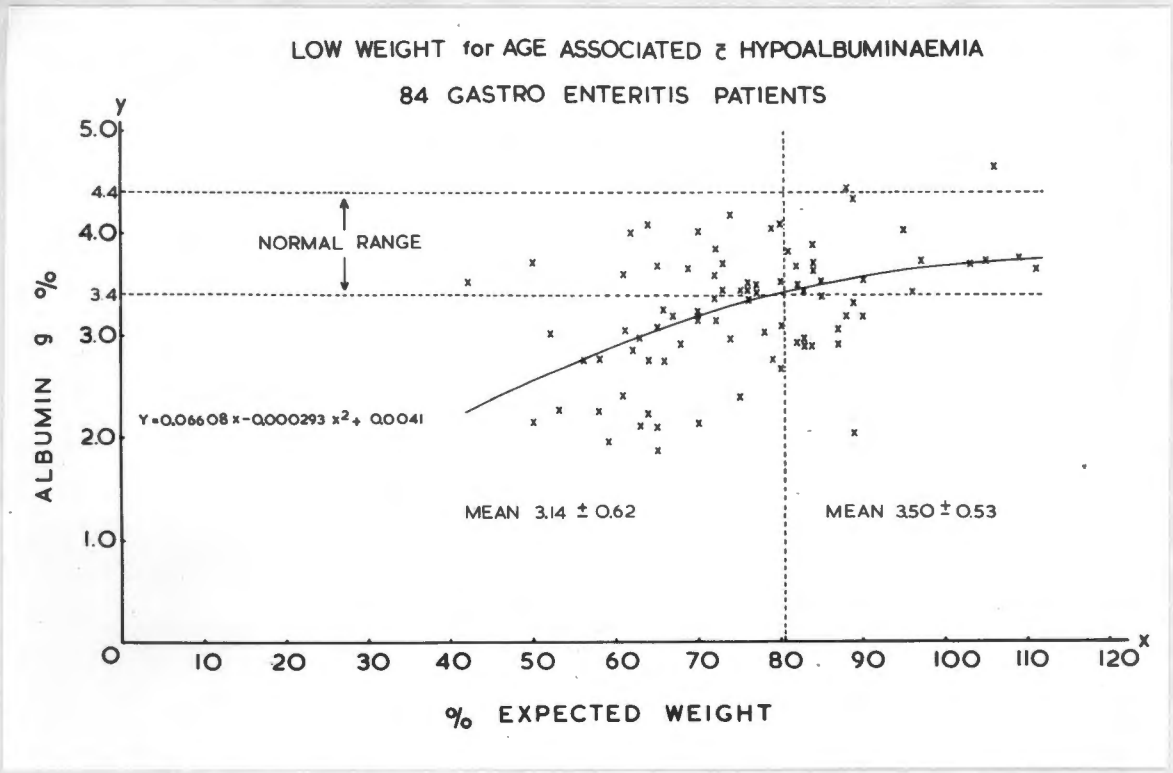
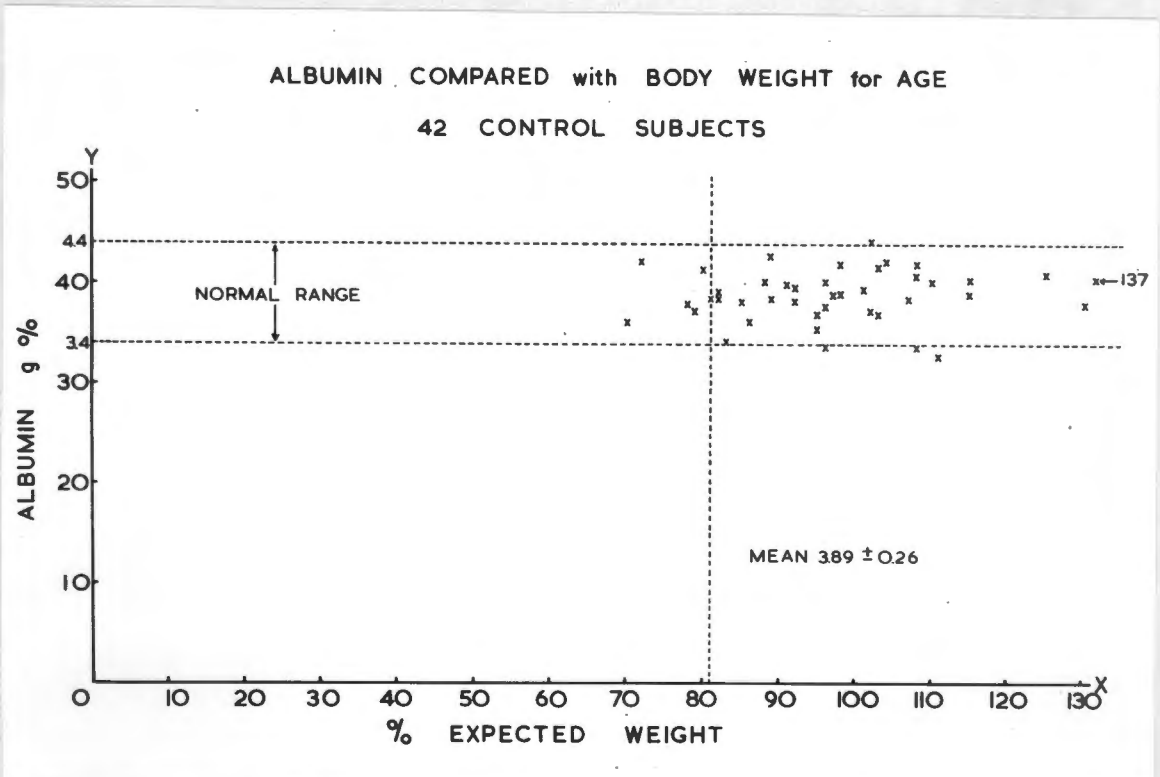



FIGURE.12.

**SERUM ALBUMIN AND WEIGHT OF CONTROL SUBJECTS.**



The incidence of hypo-albuminaemia increased significantly with advancing age. Also in the table it can be seen that the highest mean serum albumin occurred in the youngest group of patients. After the age of 9 months serum albumin of the cases was well below the lowest normal limit.

Low weight: The serum albumin after rehydration of 84 patients was compared to the percent of expected weight of these patients. There were 54 low weight and 30 normal weight patients in the group. Hypo-albuminaemia occurred in 59% and 33% respectively. The mean serum albumin of the low weight children was significantly lower than that of the normal weight children as shown in Table 10.

Table 10.

Hypo-albuminaemia in relation to low weight for age.

| | Weight for age. | |
|---|---|---|
| | Below 80% | Above 80% |
| Total No. patients. | 54 | 30 |
| Low albumin | 32 | 10 |
| Mean albumin | 3.14 ± .62 | 3.50 ± .53 |
| | t= 2.705 | p= < 0.01 |

In Figure 11. the serum albumin in grams percent is plotted against the percent expected weight of the patients. The association of hypo-albuminaemia with low weight is very clearly demonstrated. Above 90% of expected weight the serum albumin was always within the normal range. The quadratic regression line shows very strikingly how the albumin drops with increasing weight loss. In the normal weight range the albumin and weight vary independently. The association of low weight and low serum albumin was highly significant ( F 81 = 41.836 p = < 0.01).

The albumin and weight of the control subjects are shown in Fig. 12.

The only abnormal albumin value was in a child who was above the mean expected weight for age.

Hypo-albuminaemia and a low weight for age were thus very common in these children with severe dehydrating gastro-enteritis. There was a striking correlation between low weight and low serum albumin. Both occurred more frequently in the older children than in the younger patients in the series.

Oedema in relation to serum albumin and low weight for age.

On admission all patients were free of oedema. After rehydration there were 15 patients with slight oedema, of whom 8 had orbital oedema and 7 had oedema of the legs and feet which was just detectable by pitting on pressure.

There were 3 patients in whom the intravenous scalp vein infusion had leaked into the tissues to produce local oedema. They were not included in the oedema group. Over-hydration was clearly responsible for oedema in one patient only who was inadvertently given the fluid replacement too rapidly.

The mean serum albumin and mean percent expected weight of the patients who developed oedema are shown in Table 11.

Table 11.

| | Mean. | Range. |
|---|---|---|
| Serum albumin | 3.02 g% | 2.14 - 4.35 g% |
| Mean weight % | 74% | 50 - 89% |

Although the majority of patients had a low albumin and/or a low weight for age, there were exceptions. Patients with the lowest albumin did not develop oedema and one child with a high albumin did have oedema.

There was thus no clear correlation between hypo-albuminaemia and oedema in these patients.

Other signs of nutritional deficiency.

These signs are listed in relation to weight for age in Table 12.

Table 12.

| | Weight for age. | |
|---|---|---|
| | Below 80% expt. | Above 80% expt. |
| Total No.of patients | 64 | 37 |
| Skin lesions | 14 | 5 |
| Marasmus | 4 | 0 |
| Pre-kwashiorkor | 2 | 0 |
| Anaemia | 26 | 13 |
| Rickets | 6 | 3 |

Clinical diagnosis of protein-calorie malnutrition: Apart from low weight for age, a clinical diagnosis of protein deficiency could have been made in only 25% of cases i.e. by virtue of skin lesions or the appearance of marasmus or pre-kwashiorkor. Skin lesions were minimal and consisted of angular stomatitis, dry scaling over the legs and arms, slight hyper-pigmentation in exposed areas or "crazy-paving" over the shins. Five normal weight patients showed skin lesions Marasmus was present in four children who showed obvious wasting and absence of subcutaneous fat. Some of the underweight children looked deceptively well by virtue of the presence and normal distribution of subcutaneous fat. Pre-kwashiorko was diagnosed in 2 patients with growth failure, angular stomatitis, sparse hair and "moon facies". Hair changes were not accurately recorded in all cases but were never gross.

Rickets: This diagnosis was clinically made in 2 patients and radiologically confirmed in a further 7 children. The lowest weight at which rickets occurred was 72% of the expected.

Anaemia: A haemoglobin level below 10 g% after rehydration was considered an indication of anaemia at all ages in this study. At this conservative estimate

39% of patients had anaemia. (Anaemia was fully investigated in the second series in conjunction with Friedman et al.[129] A high incidence of iron deficiency and folic acid deficiency was found. $B_{12}$ deficiency did not occur).

The difference in incidence of anaemia and rickets was not striking between the two weight groups. Clear-cut clinical signs of malnutrition other than low weight were not commonly present in the group of patients studied.

The history of diarrhoea in relation to the nutritional status.

If diarrhoea had occurred previously more than twice it was considered to be recurrent.

A history of recurrence was significantly more frequent in the low weight patients. The figures are given in Table 13.

Table 13.

Recurrent diarrhoea and low weight for age were significantly associated.

| | Weight for age. | |
|---|---|---|
| | Below 80% | Above 80% |
| Total No. of patients. | 64 | 37 |
| Recurrent diarrhoae. | 30 | 7 |
| | $x^2 = 7.898$ | $p = < 0.005$ |

Almost half the low weight patients had a recurrent history and this was true in less than one fifth of the normal weight cases.

The patients with recurrent diarrhoea showed a higher incidence of hypo-albuminaemia than those with no history of recurrence, but these differences were not significant by the Chi square test ($p = < 0.20$) Table 14.

Table 14.

Hypo-albuminaemia in relation to recurrent diarrhoea.

| | Recurrent diarrhoea | No recurrence |
|---|---|---|
| Total No. patients. | 34 | 53 |
| Low albumin | 21 | 24 |
| | $x^2 = 2.256$ | $p = < 0.20$ |

The incidence of hypo-albuminaemia was also not significantly more frequent in the patients who had diarrhoea for longer than 7 days than in those with a shorter history. The mean serum albumin did not differ significantly between the two groups. These figures are shown in Table 15.

Table 15.

The duration of the illness did not significantly influence albumin concentration.

| | Duration of Present Attack. | |
|---|---|---|
| | More than 7 days. | Less than 7 days |
| Total No. patients | 23 | 64 |
| Low albumin | 13 | 32 |
| | $x^2 = 0.285$ | $p = < 0.60$ |
| Mean albumin | 3.28 ± .61 g% | 3.17 ± .63 g% |
| | $t = 0.7333$ | $p = < 0.50$ |

Of the 23 patients with diarrhoea for longer than 7 days there were 20 who had a history of 14 - 21 days.

## INFECTION.

The interpretation of microscopy and culture results is not always easy. The following notes explain the interpretation of results in this study:-

1. Enteral infection was accepted when shigella, salmonella, specific E.coli,

abundant pus cells or abundant yeasts were found.

2. During microscopic examination of the stools pus cells were recorded by 4 grades of + - ++++. "Abundant pus cells" here recorded represent the last two grades. In all the patients with shigella and in all but 2 of the salmonella cases pus cells were present in these amounts. "Abundant pus cells was accepted as evidence of enteral infection. Microscopic blood was usually present together with abundant pus in the stool but macroscopic blood was not seen.
3. Entero-bacteria other than the above were not considered here to have a causal relationship to diarrhoea and they were not accurately identified.
4. Staphylococcus aureus was looked for in the second trial but was not identifie in large numbers inmany of the stools examined.
5. Massive numbers of yeast spores and hyphae in the stools were considered pathogenic even if Candida albicans was not identified on culture. Lesser numbers were not considered as a cause of diarrhoea,
6. A causal relationship was accepted for giardia lamblia and other parasites were "doubtful" causes.
7. The diarrhoea was labelled "cause unknown" only if the stools were totally negative and the patient had no parenteral infection.
8. Multiple infection refers to the presence of more than 2 pathogens in each stool.

The findings in this section are recorded for the total number of patients of both trials.

The following general observations are necessary before an analysis of the results is given:-

(1) The isolation of shigella was twice as common in Summer (Trial II as in Trial I. which was done during the colder season of the year.

(2.) E.coli was only looked for in 45 patients and 32 control subjects of the second trial. The percentage incidence is given from these numbers.

(3) Excluding the above differences, the two trials were comparable regarding the incidence of infection.

(4) Virus studies were not done in any of the groups investigated.

The findings of stool microscopy and culture are given in Table 16, for all the patients and control subjects.

Table 16.

Findings on stool culture and microscopy.

| | Patients | Controls. |
|---|---|---|
| Total No. of cases | 101 | 43 |
| Salmonella | 7 | 5 |
| Shigella | 13 | 0 |
| E.coli | 31 | 19 |
| Abundant yeasts | 6 | 0 |
| Abundant pus cells | 55 | 5 |
| Giardia lamblia | 17 | 16 |
| Ascaris | 22 | 5 |
| Trichuris trichiura | 10 | 0 |
| Trichomonas hominis | 26 | 0 |
| Double infection | 28 | 5 |
| Multiple infection | 15 | 0 |
| Totally negative | 13 | 60 |

There were some differences between patients and controls that were very striking:-

(1) Shigella was isolated in 13% of patients and in none of the control subjects.

(2) Pus cells were found in 55% of patients and only 5% (2cases) of the controls. One control patient with pus had a salmonella and the other had pus cells only.

(3) There was also a striking difference in the incidence of parasites between patients and controls, excluding giardia lamblia.

(4) Multiple infection did not occur in the controls but it was present in 15% of patients.

(5.) Bacteriological examination was totally negative in 60% of control subjects and in only 13% of patients.

It is interesting to note that salmonella and giardia lamblia occurred with almost equal frequency in patients and control subjects. Although E.coli occurred more frequently in the patients, the difference in incidence between patients and controls was not statistically significant by the Chi square test.

The most striking feature of the patients with gastro-enteritis was the small percentage of stools that were totally negative.

The occurrence of a large number of pus cells was a striking finding. It was almost invariably present when shigella or salmonella was isolated, but none of the other findings could be significantly associated with the presence of pus in the stools.

Trichomonas hominis although frequently present, was found by itself in only 6 patients and could not be assessed separately.

Relating the incidence of positive stool findings to the nutritional status of the patients showed up some differences.

In Table 17 these findings together with the incidence of parenteral infection are indicated in relation to the degree of malnutrition by weight.

Table 17.

Infection in relation to nutritional status.

| | Degree of malnutrition by weight. | | | | |
|---|---|---|---|---|---|
| | 3rd | 2nd | 1st | Normal | Total |
| Total No.patients | 10 | 38 | 42 | 11 | 101 |
| Enteral infection | 9 | 24 | 29 | 7 | 69 |
| Worms | 3 | 13 | 7 | 1 | 24 |
| Worms and/or Giardia | 4(40%) | 21(55%) | 10(24%) | 1(9%) | 36 |
| Trichomonas | 2 | 14 | 7 | 3 | 26 |
| Multiple infection | 4(40%) | 8(21%) | 3(7%) | 0 | 15 |
| Oral thrush | 2 | 3 | 6 | 0 | 11 |
| Herpes stomatitis | 1 | 0 | 0 | 0 | 1 |
| Septicaemia | 1 | 0 | 0 | 0 | 1 |
| Tuberculosis | 1 | 0 | 0 | 0 | 1 |
| Pneumonia | 1 | 3 | 1 | 0 | 5 |
| U.R.T. infection | 0 | 3 | 0 | 0 | 3 |
| Skin sepsis | 1 | 0 | 2 | 0 | 3 |

The small number of normal weight children makes it difficult to draw comparisons with the malnourished but this can be done between the more grossly abnormal and those less abnormal in weight.

Enteral infection as defined, occurred in 69% of patients. It was not more frequently found in malnourished than in the wellnourished patients.

Multiple infections and intestinal parasites, however, did occur with much greater frequency in the more grossly underweight patients.

Parenteral infection was not common in this series (14%) but tended to be more frequently present in those who were malnourished. Septicaemia was present in only one patient. It so happened that all the patients with parenteral infection also had a positive finding in the stools. It did not therefore increase the overall incidence of infection.

In Table 18 the incidence of some findings is shown for the different age groups of patients.

Table 18.

Intestinal parasites and pathogens in relation to age.

| | Age in months. | | | | |
|---|---|---|---|---|---|
| | 0 - 3 | 4 - 9 | 10 - 15 | Over 15 | Total |
| Total No. patients | 13 | 43 | 21 | 24 | 101 |
| Enteral infection | 8(61%) | 30(88%) | 12(51%) | 19(79%) | 69 |
| E.coli | 1 | 9 | 3 | 1 | 14 |
| Ascaris | 0 | 3 | 5 | 14 | 22 |
| Trichuris trichiura | 0 | 1 | 2 | 7 | 10 |
| Giardia | 1 | 4 | 4 | 8 | 17 |
| Worms and/or giardia | 1 | 7(16%) | 8(38%) | 20(83%) | 36 |

Differences were apparent in the incidence of E.coli and parasites. E.coli occurred in the younger patients but was isolated only once in children over 1 year.

Worms and flagellates occurred with increasing frequency in the older children. After the age of 15 months only 17% of patients were free of worms and giardia. It occurred once under 4 months.

The influence of age and nutritional status cannot be clearly separated in relation to infection. In general the older patients were more malnourished and had a high incidence of enteral plus parasitic infection.

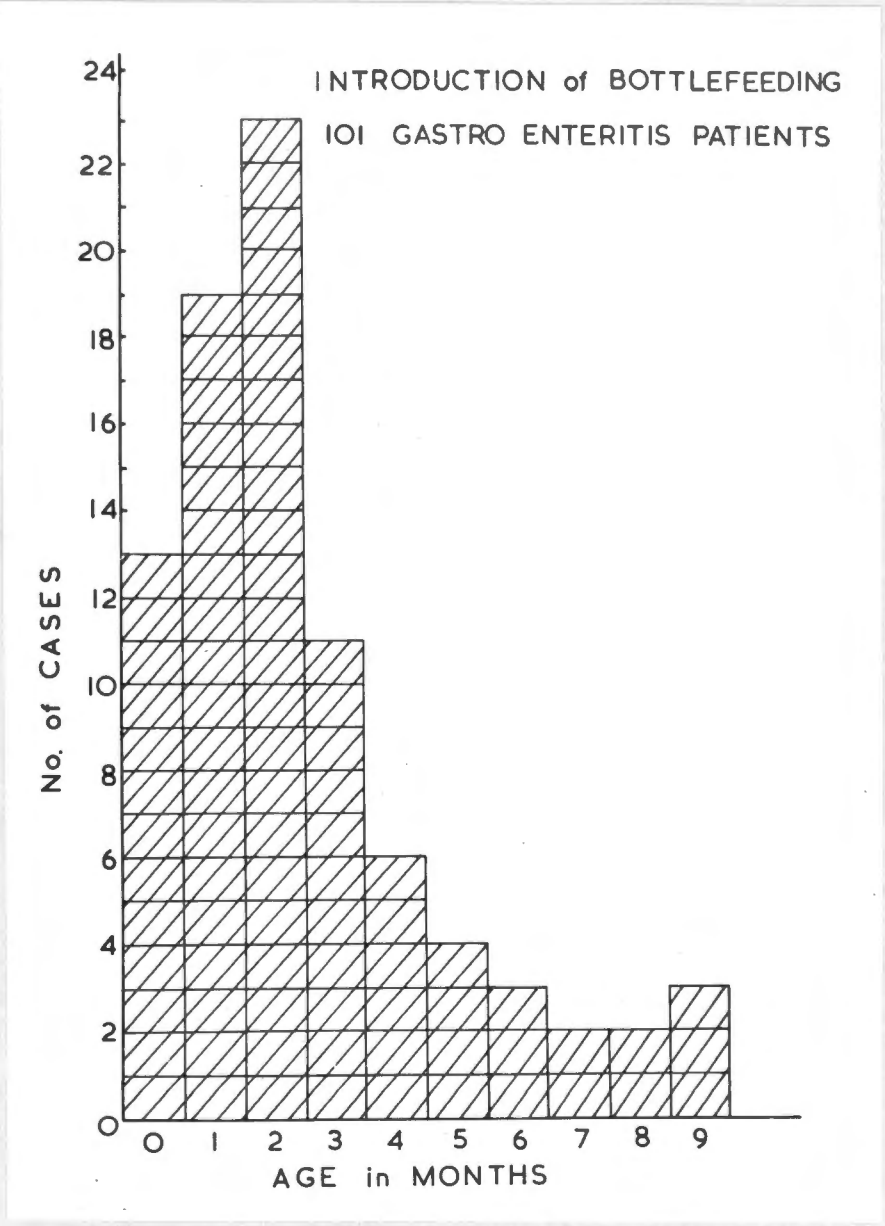
Of the 36 patients with worms and giardia, 28 were low weight and 23 of these were older than 9 months. Of the 8 normal weight children in this group 5 were older than 9 months.

Of the 69 patients with enteral infection 44 were low weight and 24 of these were older than 9 months. Of the 25 normal weight children in this group 7 were older than 9 months.

Enteral infection thus seemed to be fairly evenly distributed between the ages and weight groups. Parasites were much more common in the

FIGURE. 13.

AGE WHEN BOTTLE-FEEDING WAS INTRODUCED.



older patients and possibly more common in the malnourished, regardless of age. These findings are summarised in Table 19. For each of two age groups the incidence of parasites and infection are given for the normal and low weight children.

Table 19.

| | Age in months. | | | |
|---|---|---|---|---|
| | 0 - 9 | | Over 9 | |
| | < 80% Expt.wt. | > 80% Expt.wt. | < 80% Expt.wt. | > 80% Expt.wt. |
| Total No. of patients. | 29 | 27 | 35 | 10 |
| Enteral Inf. | 20 | 18 | 24 | 7 |
| Worms & giardia | 5 | 3 | 23 | 5 |

Of the 14 E.coli isolations 9 were in the low weight young children. The significance of this finding is doubtful, due to the small number of cases.

## SOCIO-ECONOMIC ASPECTS OF THE STUDY.

This part of the study was done together with the Social Worker Miss Moodie.[130] Some of the relevant findings will be indicated here.

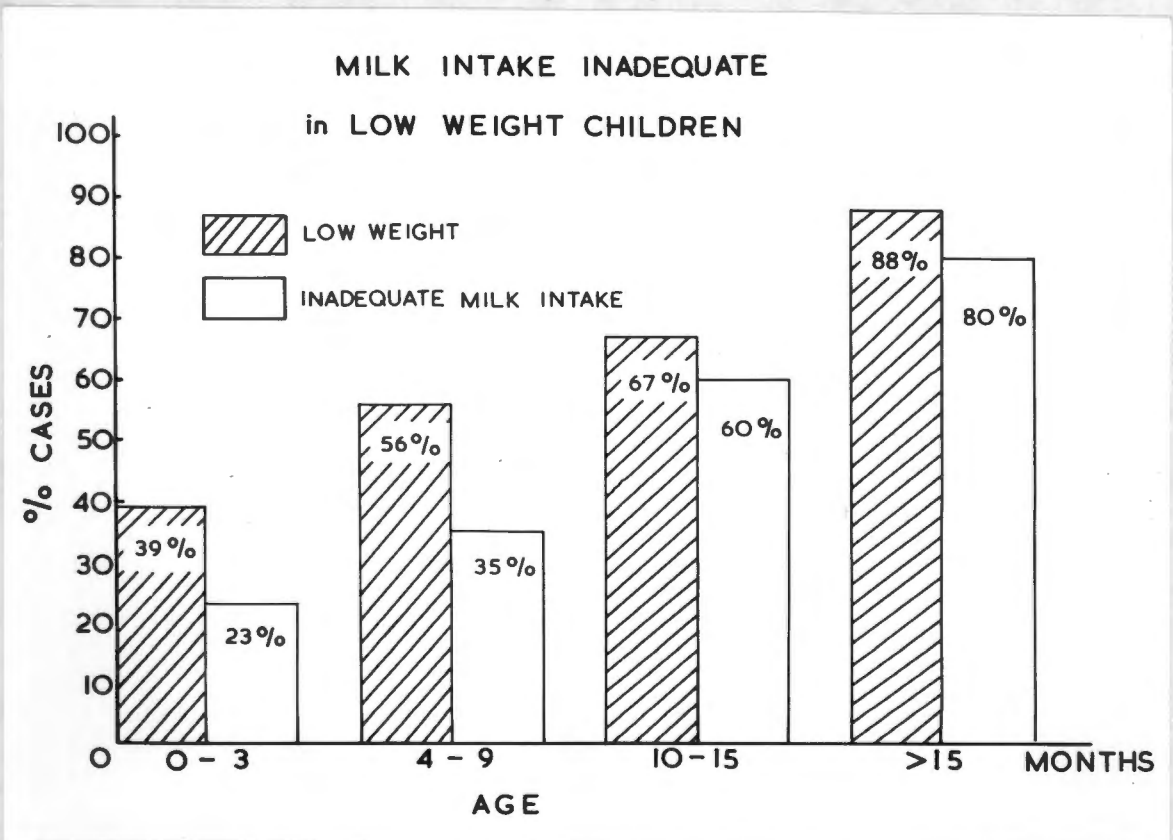
The majority of children seldom or never attended the child welfare centres. The mothers were often ignorant of proper child care and feeding requirements.

Milk intake dropped sharply with advancing age after breast feeding had been discontinued.

At the age of 3 months 66%of children had been partly or totally weaned from the breast. The first attack of diarrhoea almost invariably followed the introduction of bottle feeds. In Fig. 13 the age at which bottle feeding was introduced is shown. The majority of malnourished children had

FIGURE. 14.

LOW WEIGHT FOR AGE OCCURRED IN THE CHILDREN WHO DID NOT GET ENOUGH MILK.



been receiving less than half a pint of milk per day. In Fig.14 the percent of cases with an inadequate milk intake in 4 age groups is shown, togther with the percent of patients who were underweight for age in the age group. Note the very close similarity between the two and the striking stepwise increase with advancing age.

Judged by accepted criteria, poverty was common throughout the series and often extreme in degree. Although many cases came from housing estates with available tap-water and adequate water-borne sewage disposal, the standard of personal and environmental hygiene was often very poor indeed. The socio-economic pattern was less homogeneous for the younger patients than was found in a kwashiorkor study.[131]. However, in the older age groups the similarity was so great that no distinction could be drawn between the gastro-enteritis and kwashiorkor studies.

Effective care of the infant depended upon the availability of the mother in the home and on her competence. The latter was assessed on evidence of her handling of the patient, her success with previous children, her ability to learn by experience, her use of community facilities, management of the family budget and on the impression she made as regards general intelligence and maturity. It was found that over the whole series the most capable mothers had children with better weights than the others. The capable mothers failed only where poverty was most extreme.

Immediate results of treatment and the follow-up study.

Immediate results of therapy: In assessing the results of antibiotic therapy one had to rely on the history from the mother regarding the duration of the diarrhoea. No correction was applied to the mortality rate.

Failure of therapy was assessed in the following way:-

1. Death within a week of admission.
2. If treatment was changed the therapeutic result was recorded as a failure.

This was only done on 2 occasions.

3. If diarrhoea continued beyond 1 week of admission. The number of stools per day was not used as a criterionbecause information was not reliable,

Therapy was considered successful if diarrhoea stopped within a week and the patients remained free of diarrhoea for the next week, that is, the patient was free of diarrhoea for the major part of the first 2 weeks after admission. This was done in an attempt to allow for daily fluctuations and to minimise bias. Stool cultures repeated on the 3rd day of treatment were negative in all but 3 patients. Two of these had salmonella and one shigella.

On the above criteria 54 patients responded to therapy and 47 failed to respond. The majority of normal weight children responded to therapy and, as weight loss increased the treatment failed with greater frequency. Of the patient who were 2nd and 3rd degree malnourished by weight, only 35% responded to treatment In Table 20 the number of failures are shown in relation to the total number of patients in each of 3 groups of malnutrition and normal weight for age.

Table 20.

Response to antibiotic therapy in all patients related to weight for age.

| | Malnutrition by weight | | | |
|---|---|---|---|---|
| | 3rd Degree | 2nd Degree | 1st Degree | Normal |
| Total No.patients | 10 | 38 | 42 | 11 |
| Failed to respond | 9(90%) | 22(58%) | 11(26%) | 5(45%) |

There were 52 patients on Chloromycetin palmitate and 49 on Penicillin and Sulphadiazine. In Table 21 the results are compared between these two groups of patients.

Table 21.

Comparing the règimes of treatment.

| | Chloromycetin | Penicillin & Sulphadiazine |
|---|---|---|
| Total No. patients | 52 | 49 |
| Failed to respond | 31 | 16 |
| | $x^2 = 7.370$ | $p = < 0.01$ |

On Chloromycetin 60% of patients failed to respond and on Sulphadiazine and Penicillin 33% did not respond. The difference was highly significant.

On further analysis this difference was apparent in the malnourished patients with enteral infection while the results were comparable between the two règimes in other respects. Failure was common in the low weight patients in both groups. In Table 22 the results are compared between the drugs in the low weight patients with infection.

Table 22.

Comparing the drugs in low weight patients with enteral infection

| | Chloromycetin | Penicillin & Sulphadiazine |
|---|---|---|
| Total No. patients below 80% expt.wt. | 16 | 24 |
| Failed to respond | 12 | 9 |
| | $x^2 = 5.4135$ | $p = < 0.05$ |

Here infection included the finding of salmonella, shigella, E.coli and abundant pus cells. The numbers involved are small but the difference in favour of Penicillin and Sulphadiazine was significant. Weight for age was comparable

DETAILS OF PATIENTS WHO DIED.

| NAME | AGE MONTHS | %EXPT.WT. | ALBUMIN % | HAEMOGLOBIN % | X-RAY | STOOL | DURATION OF ILLNESS DAYS | PREVIOUS HISTORY OF DIARRHOEA | INTERVAL BEFORE DEATH | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|
| L.M. | 7 | 50 | 3.73 | 7.8 | Nil | Salmonellae Giardia Ascaris | 14 | Recurrent Diarrhoea and I.V. therapy. | 7 days | Died at home with continuous Diarrhoea |
| L.Z. | 7 | 58 | 2.26 | 8.6 | Nil | Yeasts | 21 | Recurrent Diarrhoea | 4 months | Died at home with recurrent Diarrhoea and Vomiting. |
| A.M. | 14 | 58 | 2.78 | 9.7 | Nil | Shigellae Trichomonas hominis. | 4 | Recurrent Diarrhoea | 4 months | Admitted to hospital with Kwashiorkor after 4 months. |
| J.G. | 14 | 59 | 1.97 | 10.1 | Nil | Yeasts | 7 | Nil | 4 days | Very ill with continued Diarrhoea and Vomiting. |
| C.F. | 17 | 50 | 2.15 | 8.2 | Tuber-culosis | E.coli Giardia | 14 | Recurrent Diarrhoea | 2 days | Pulmonary Tuberculosis. |
| D.R. | 19 | 61 | 2.41 | 8.2 | Nil | Salmonellae Ascaris Trichuris Trichiura. | 7 | Nil | 4 days | Continued Diarrhoea and I.V. therapy. |
| C.A. | 3 | 64 | 3.85 | 10.25 | Nil | Pus | 4 | Mild recurrent Diarrhoea | 2 months | Died at home. No details known. |
| A.D. | 19 | 65 | 2.11 | 12.2 | Nil | Pus Ascaris | 7 | Mild recurrent Diarrhoea | 3 weeks | Repeated I.V.therapy. Developed Kwashiorkor. |
| R.B. | 17 | 73 | 2.48 | 9.7 | Nil | Negative | 7 | Recurrent Diarrhoea. Had Kwashiorkor months before. | 2 days | Admitted to hospital. Continued I.V.therapy. |
| M.K. | 4 | 74 | 2.98 | 9.6 | Nil | Giardia | 6 | Mild recurrent Diarrhoea | 4 months | Recurrent Diarrhoea. Died at home. |
| C.J. | 7 | 80 | - | 10.24 | Nil | Negative | 1 | 1 Mild attack | 1 day | Continued I.V therapy. Very ill on admission. |
| M.O. | 9 | 89 | - | 10.25 | Nil | Pus Giardia | 3 | Recurrent Diarrhoea | 4 days | Repeated I.V therapy. Continued Diarrhoea and Vomiting. |
| C.M. | 8 | 96 | - | 9.51 | Nil | Trichomonas hominis | 2 | 1 Mild attack | 1 day | Hyperosmolarity with Saggital Sinus thrombosis. |
| B.J. | 3 | 97 | 3.74 | 12.95 | Nil | Pus Trichomonas hominis | 14 | Nil | 5 days | Continued I.V. therapy. |

TABLE.24.

DETAILS OF 14 PATIENTS WHO DIED.

between the groups who failed or responded. In Table 23 the number of patients who responded or failed are shown for each drug in the normal and the low weight groups.

Table 23.

Weight for age in patients on Chloromycetin or Penicillin and Sulphadiazine.

| | Chloromycetin | | Pen. & Sulpha. | |
|---|---|---|---|---|
| | Responded | Failed | Responded | Failed. |
| Total No. below 80% expt.wt. | 10 | 22 | 19 | 13 |
| Mean % expt.wt. | 74 ± 5 | 65 ±10 | 71 ± 8 | 64± 10 |
| Total No. above 80% expt.wt. | 11 | 9 | 14 | 3 |
| Mean % expt. wt. | 89 ± 9 | 94 ± 9 | 90 ± 7 | 85 ± 11 |

The mean percent expected weight for each group is indicated. The patients who failed to respond were more grossly underweight in both groups but a smaller percentage of low weight children responded to Chloromycetin than to Penicillin and Sulphadiazine.

Mortality: The details of the 14 patients who died are summarised in Table 24.

Three children died within 48 hours, a further 7 died within a week and 4 died after an interval of a month or more. The immediate mortality was 10%.

Of the children who died only one was under 4 months. Of the 6 who were over a year old all were grossly malnourished by weight and had serum albumin levels below 3 g%. Only 3 of the children who died were normal in weight. Infection was not more frequent in the patients who died than in the whole series. Table 25 gives an analysis of deaths on the different antibiotic regimes. Of the patients on Chloromycetin 7 died within a week and 5 of these

were grossly malnourished. Two patients on Penicillin and Sulphadiazine died within a week and neither was grossly malnourished.

Table 25.

Deaths in patients on different antibiotic regimes.

| Name | Age months | Interval before death days. | Wt.% | Albumin | Stool. | Comments. |
|---|---|---|---|---|---|---|
| Chloromycetin. | | | | | | |
| L.M. | 7 | 7 | 50 | 3.73 | Sal.G.Asc. | Had prolonged recurrent diarrhoea. |
| D.R. | 19 | 4 | 61 | 2.41 | Sal.Asc. T.T. | Short history. Severe diarrhoea. |
| C.F. | 17 | 2. | 50 | 2.15 | E.coli.G. | Pulmonary tuberculosis. Recurrent diarrhoea. |
| J.G. | 14 | 4 | 59 | 1.97 | Yeasts | Short history. Severe diarrhoea. |
| R.B. | 17 | 2 | 73 | 2.48 | - | Recurrent diarrhoea. |
| C.M. | 8 | 1 | 96 | - | T.H. | Gross electrolyte disturbance and sinus thrombosis. |
| B.J. | 3 | 5 | 97 | 3.74 | P. T.H. | Long history. Severe diarrhoea. |
| Penicillin & Sulphadiazine. | | | | | | |
| C.J. | 7 | 1 | 80 | - | - | Short history.Severe diarrhoea. |
| M.O. | 9 | 4 | 89 | - | P. G. | Recurrent history. Severe diarrhoea. |

Sal. - salmonella. T.T. - Trichuris trichiura.
G. - giardia. T.H. - Trichomonas hominis.
Asc. - Ascaris. P. - Pus.

Although infections seldom occurred purely by themselves some general trends are apparent on analysing the results of the three entero-pathogenic bacteria.

Salmonella cases tended to have recurrent or prolonged diarrhoea and the immediate results of treatment were poor in all cases. Two of the 7 cases died.

Shigella had a better prognosis generally and response to treatment was good except in the low weight children on Chloromycetin.

E.coli had a good prognosis and immediate results were good in

respsonse to either drug règime.

## LONG TERM RESULTS IN THE GASTRO-ENTERITIS TRIALS.

A one year follow-up study was done on 80 of the original 101 patients. In addition to the 14 patients who died there were 7 who left Cape Town and could not be followed.

The main features of the follow-up study are summarised in Table 26.

Table 26.

**Aspects of follow-up study in relation to weight for age on admission to series.**

| | Below 80%expt.wt. | Above 80% expt.wt. |
|---|---|---|
| Total No. patients on admission. | 64 | 37 |
| Died | 11 (17%) | 3 (8%) |
| Lost | 2 | 5 |
| Followed for 1 year | 51 | 29 |
| Developed kwashiorkor | 10 (20%) | 2 (7%) |
| Recurrent diarrhoea - mild | 6 | 11 |
| Recurrent diarrhoea- severe | 35 (69%) | 10 (34%) |
| No subsequent diarrhoea | 10 (20%) | 8 (28%) |
| Lost weight or failed to improve | 33 (65%) | 4 (14%) |
| Normal weight after 1 year | 16 (31%) | 25 (86%) |
| Prolonged hospital treatment | 7 | 2 |
| Failed to do well | 44 (71%) | 7 (22%) |

The patients were divided into two groups according to the weight for age on admission to the series.

Originally there were 64 patients below 80% of expected weight and 37 above 80%. Mortality was 17% in the low weight group and 8% in the normal weight patients. The follow-up was completed on 51 low weight and 29 normal weight children. There were 20% of the former and 7% of the latter group who developed kwashiorkor during this time. Recurrent diarrhoea was common in both groups but severe recurrent diarrhoea was much more common in the low weight

patients (69%) as compared to the normal weight patients (34%). Only 1/5 - 1/4 of the patients had no diarrhoea after admission. Of the low weight children 65% failed to improve or lost further weight compared with 14% of the normal weight children. After a year 31% of the low weight patients had gained weight into the normal percentile range. By the end of the year 71% of these children had either died or failed to show any improvement compared to 22% of normal weight children. Many of those who improved were repeatedly treated or had been in hospital for prolonged periods before any improvement was seen.

The diarrhoea history is shown in Table 27 for all cases before and after admission to the series.

Table 27.

Diarrhoea history before and after admission to the series.

| | Below 80% expt.wt. | Above 80% expt.wt. |
|---|---|---|
| Total No. of patients | 64 | 37 |
| No previous diarrhoea | 25 (39%) | 25 (68%) |
| One or two previous attacks | 9 | 5 |
| Previous recurrent diarrhoea | 30 (47%) | 7 (19%) |
| Previous I.V. therapy | 6 | 1 |
| No subsequent diarrhoea | 10 | 8 |
| One or two subsequent attacks | 6 | 11 |
| Subsequent recurrent diarrhoea | 35 (69%) | 10 (34%) |
| Subsequent I.V. therapy | 17 (32%) | 6 (18%) |
| Recurrence before or after | 44 (69%) | 17 (45%) |

Multiple episodes of diarrhoea were present in more than half the patients, and the low weight patients very frequently had severe repeated episodes of diarrhoea. The high incidence of repeated intravenous drip gives an indication of the sexverity of the disease. Almost 1/3 of the patients needed more than one intravenous drip.

Bacteriology was not repeated at follow-up but a history of worms was always enquired about. Excluding the original 22 cases in whom worms were found a further 21 gave a definite history of Ascaris infestation.

FIGURE. 15.

WEIGHT FOR AGE AT FOLLOW-UP, BOTH SERIES.

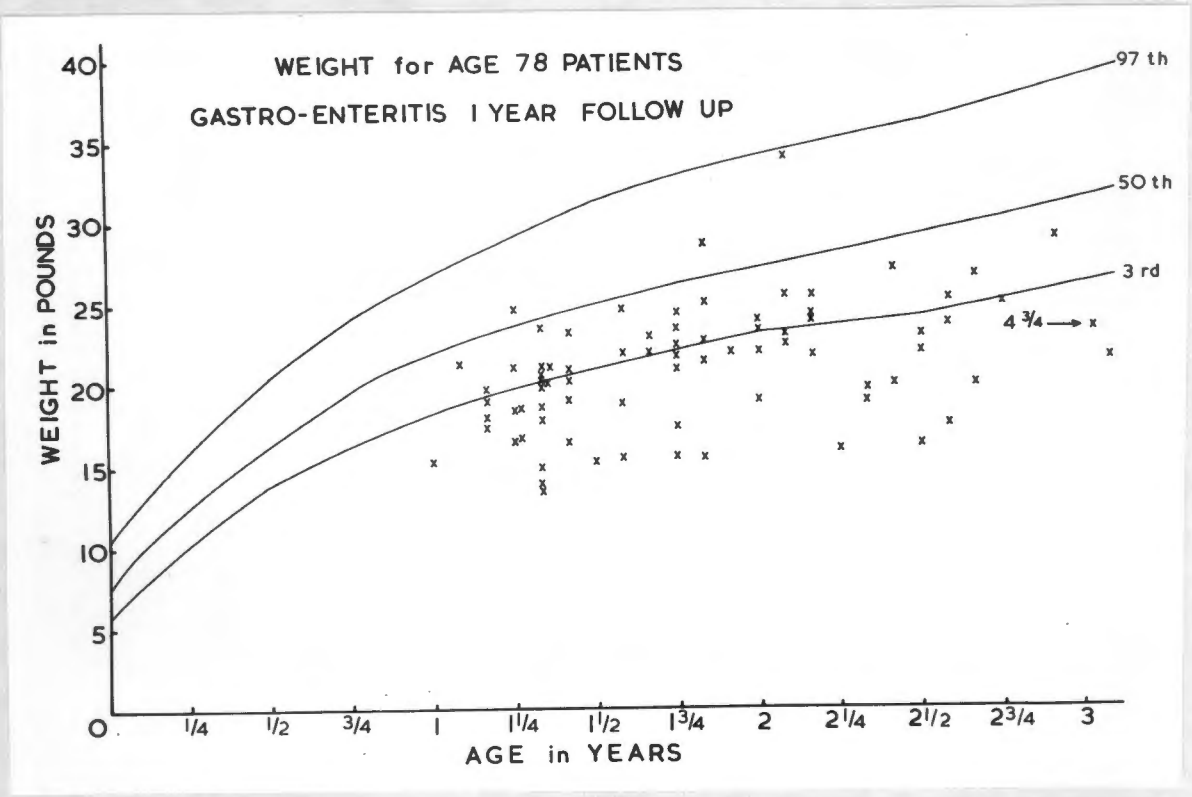



FIGURE. 16.

HEIGHT AT FOLLOW-UP - SERIES II.

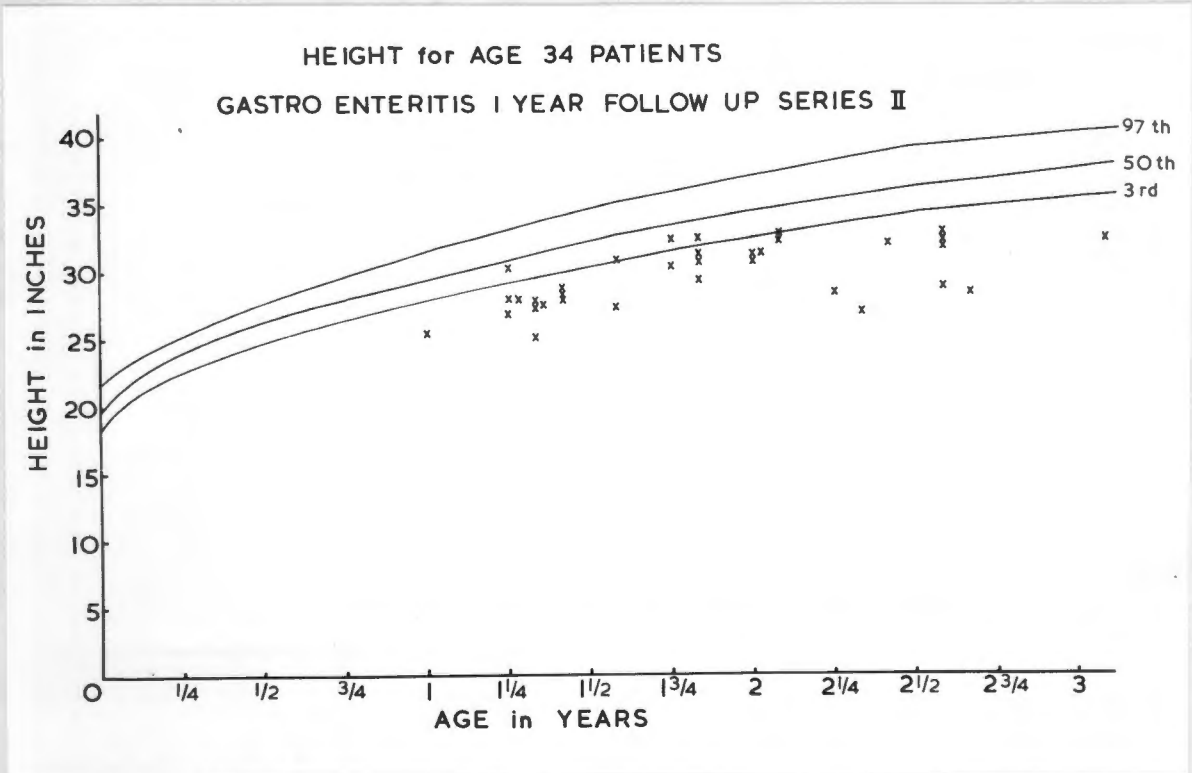
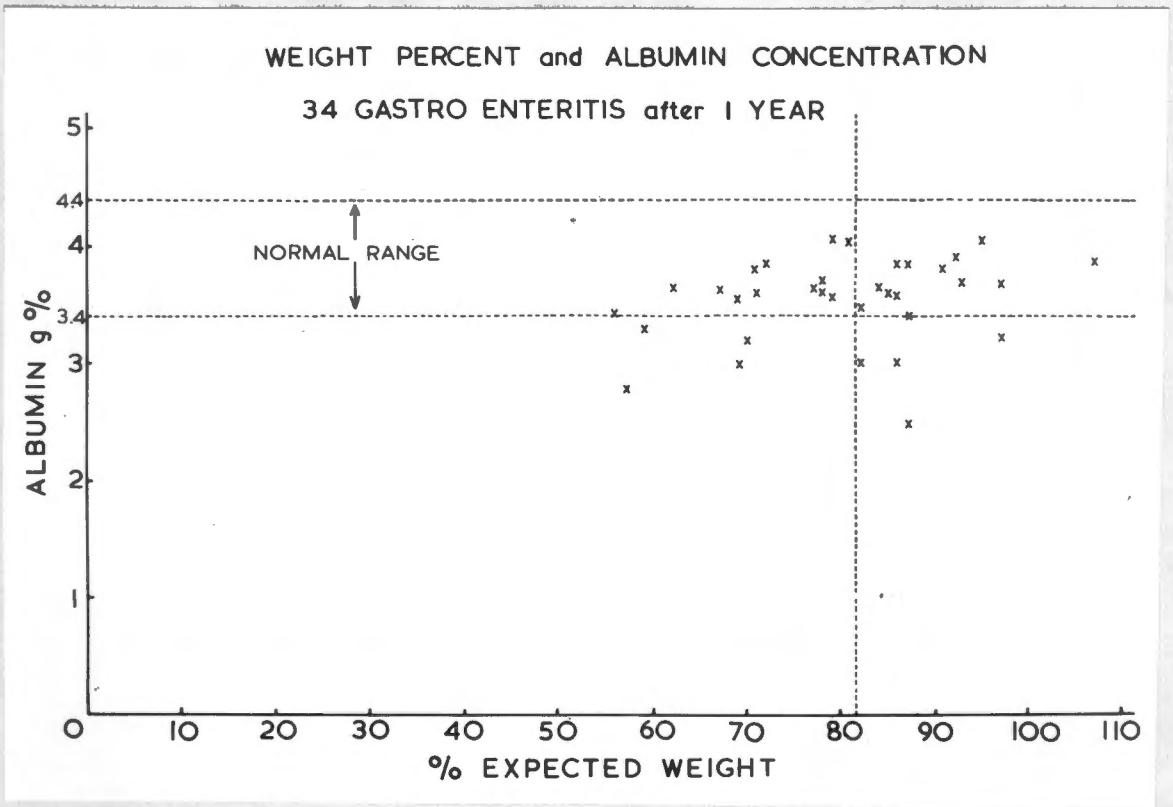


FIGURE. 17.

SERUM PROTEINS AND WEIGHT AT FOLLOW-UP - SERIES II.



The total incidence over the year was thus 43% (at least).

The weight at follow-up is shown in Figure 15. Of the 78 recorded weights 37 were less than 80% of the expected weight. The gross degree of low weight of some patients is clearly seen.

The height of the children measured in the 2nd series at follow-up is shown in Figure 16. Note the gross degree of deviation from the normal in many of the patients. All the low weight children were below the normal height range.

The follow-up serum proteins of the second trial after a year are shown in Figure 17. Only 23% of patients had a low albumin value at this stage and only one of those patients was above 90% of expected weight.

Social history at follow-up: This will be reported in detail elsewhere[130] but two relevant aspects are recorded here:-

I. In the low weight patients who gained weight into the normal percentile range there was either an improvement in the socio-economic circumstances or they received prolonged hospital treatment or came under regular clinic care.

II. The normal weight patients who deteriorated had evidence of adverse changes in the home environment.

## SUMMARY OF THE GASTRO-ENTERITIS TRIALS.

The most outstanding feature in the study was the high incidence of malnutrition in the series. This was judged by growth failure and serum albumin levels. A striking correlation between weight deficit and hypo-albuminaemia was demonstrated. Malnutrition was associated with inadequate milk intake and poor socio-economic circumstances in the family.

Morbidity both before and after admission to the series was highest in the malnourished children and they had the highest mortality rate. The older

children were more grossly malnourished than the younger and after the age of 15 months very few children with normal weights had diarrhoea.

Although there was often strongly suggestive evidence of infection, specific pathogens were not very frequently isolated. The majority of older children had either worms or Giardia or both. Multiple infections occurred most commonly in the older more malnourished children.

Results of treatment were not very satisfactory and were especially poor in the grossly underweight children. Chloromycetin palmitate in these cases gave poorer results than Penicillin and Sulphadiazine.

FIGURE.18.

AGE DISTRIBUTION NORMAL WEIGHT SYMPTOM-FREE CONTROLS.

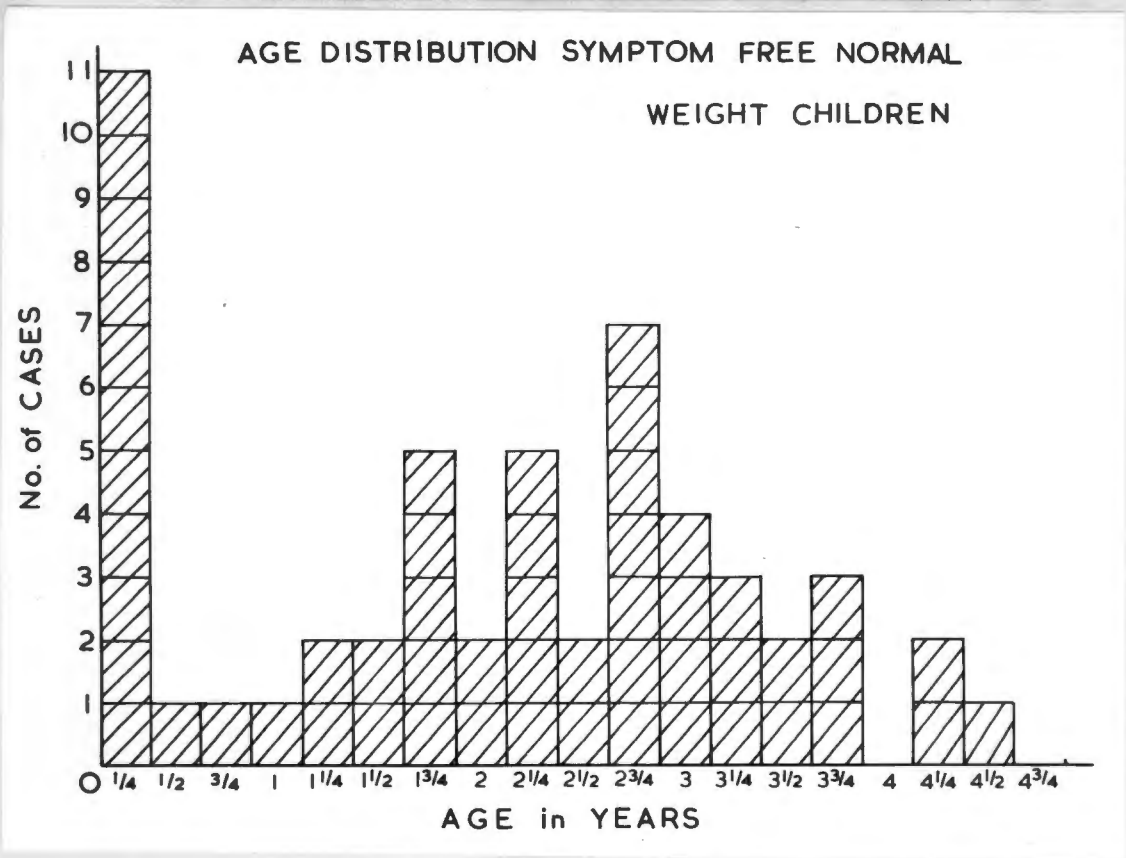



FIGURE 19.

AGE DISTRIBUTION LOW WEIGHT SYMPTOM-FREE CONTROLS.

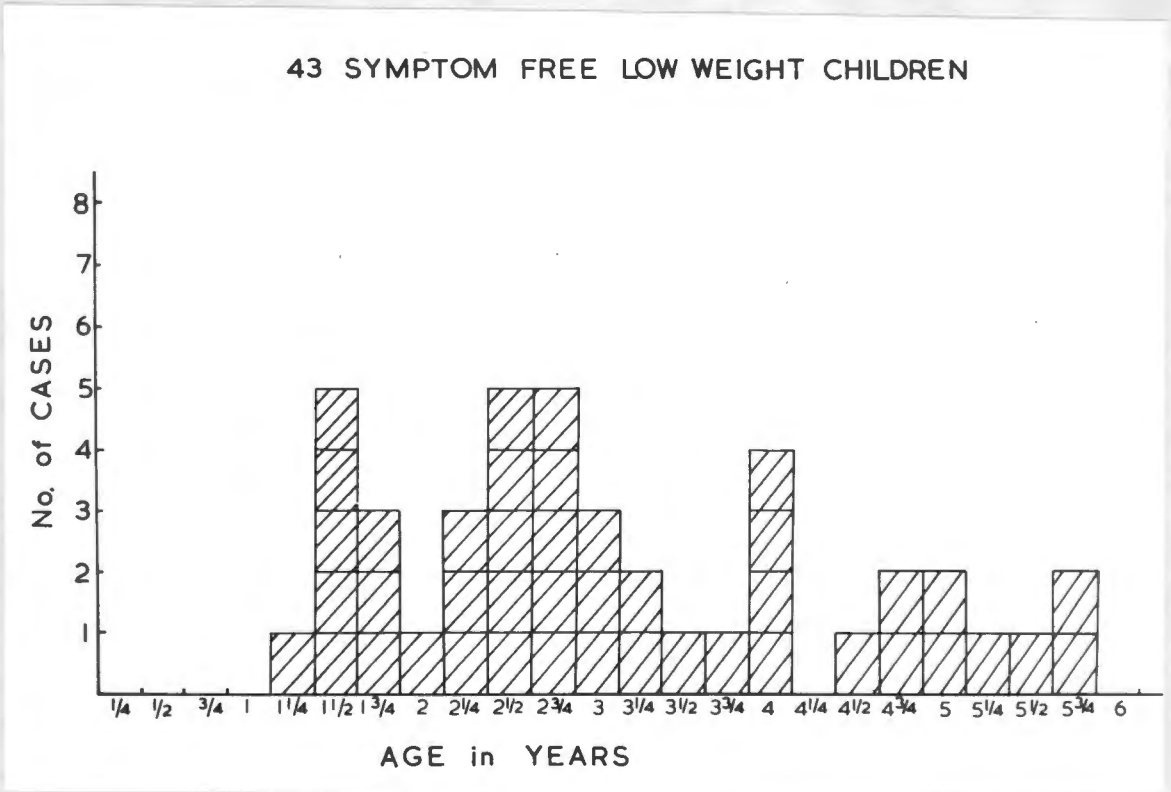


FIGURE. 20.

WEIGHT FOR AGE LOW WEIGHT CONTROLS.

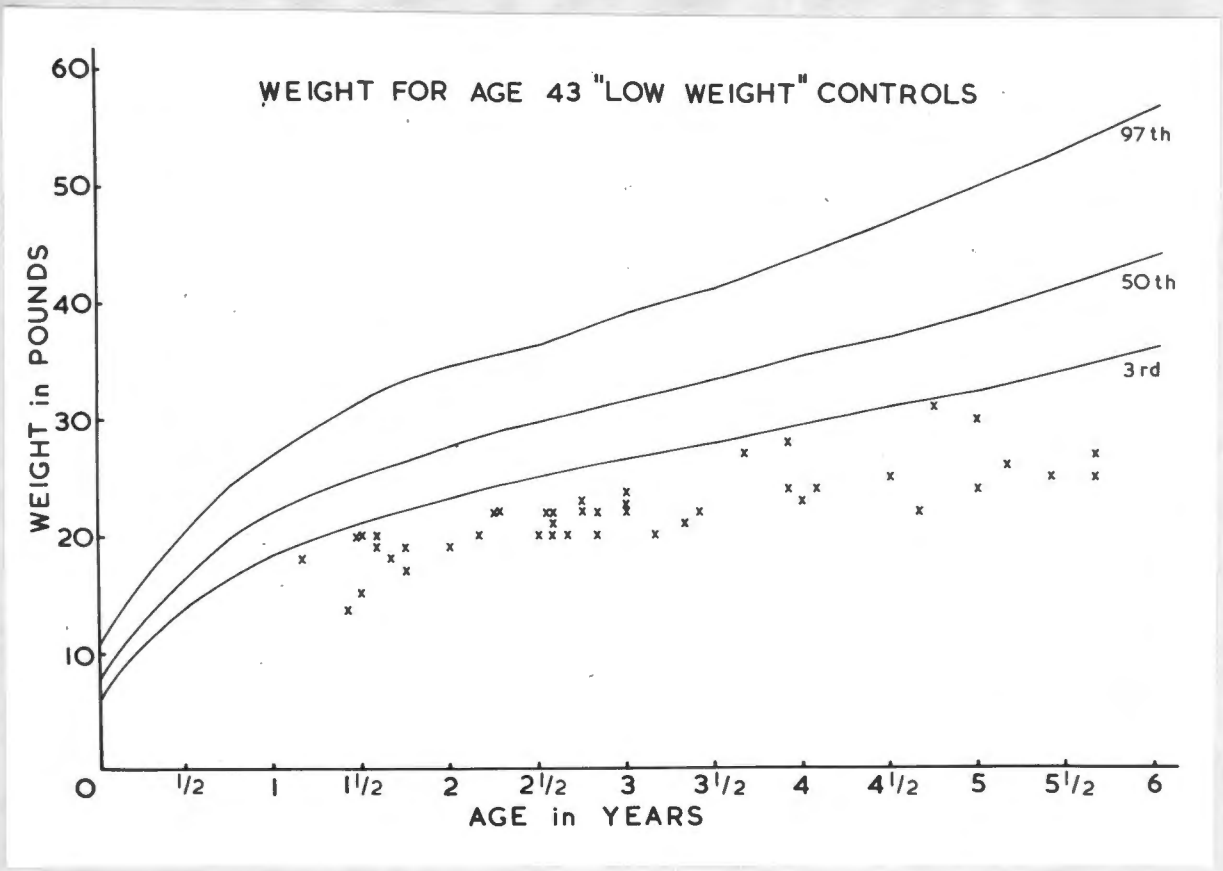
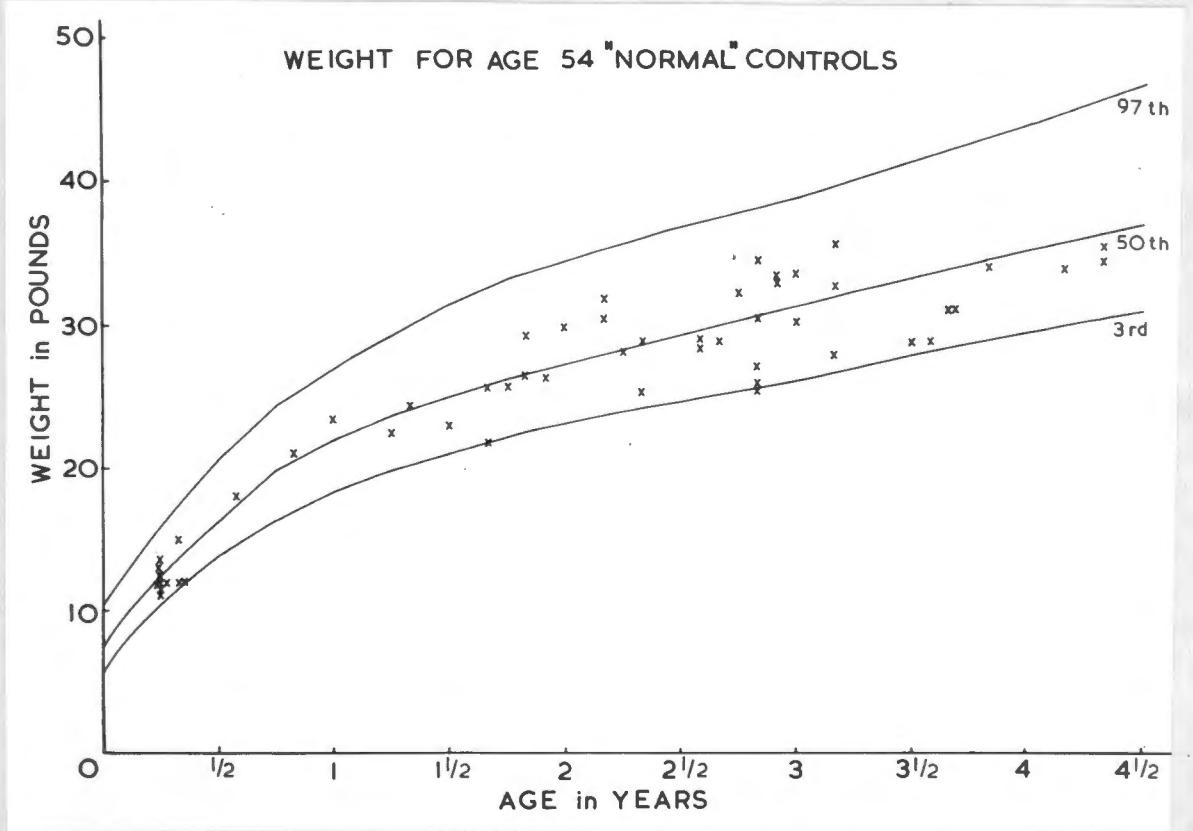



FIGURE. 21.

WEIGHT FOR AGE NORMAL WEIGHT CONTROLS.



## THE CONTROL STUDY ON GROWTH FAILURE AND NUTRITIONAL STATUS IN PATIENTS WITHOUT DIARRHOEA.

Body weight and serum albumin were recorded in 97 symptom-free non-White children. There were 43 low weight and 54 normal weight children between the ages of 3 months and 6 years.

The age distribution of each group is shown in Figs. 18 and 19. The majority of children are in the age beyond which gastro-enteritis has a peak incidence.

The normal weight group included 11 infants of 3 months (Fig.19). Very young low weight infants were not included in the study (Fig.18) because serum albumin at that age might normally be lower than in older children regardless of weight for age which was the primary consideration in this study.

The weight of each child in the respective groups is indicated by a cross against the background of the Boston percentile range in Figs. 20 and 21. In the low weight children (Fig.20) it is noticed that the older children tend to be further away from normal than the younger.

The serum albumin concentration of the 54 normal weight children was used to determine the normal range for the method used in this study (method C).

A value more than 2 standard deviations below the mean of this was considered abnormal (3.5 g%). In Table 28 the mean values and the range of albumin for each of the 2 groups are shown.

Table 28.

| | Serum albumin g% | |
|---|---|---|
| | Mean | Range. |
| Below 80% expt. Wt. | 3.22 ± .41 | 2.27 - 4.08 |
| Above 80% expt. Wt. | 4.03 ± .29 | 3.24 - 4.58 |
| | t = -11.497 | p = < 0.001 |

FIGURE. 22.

HYPO-ALBUMINAEMIA CORRELATED WITH LOW WEIGHT FOR AGE.

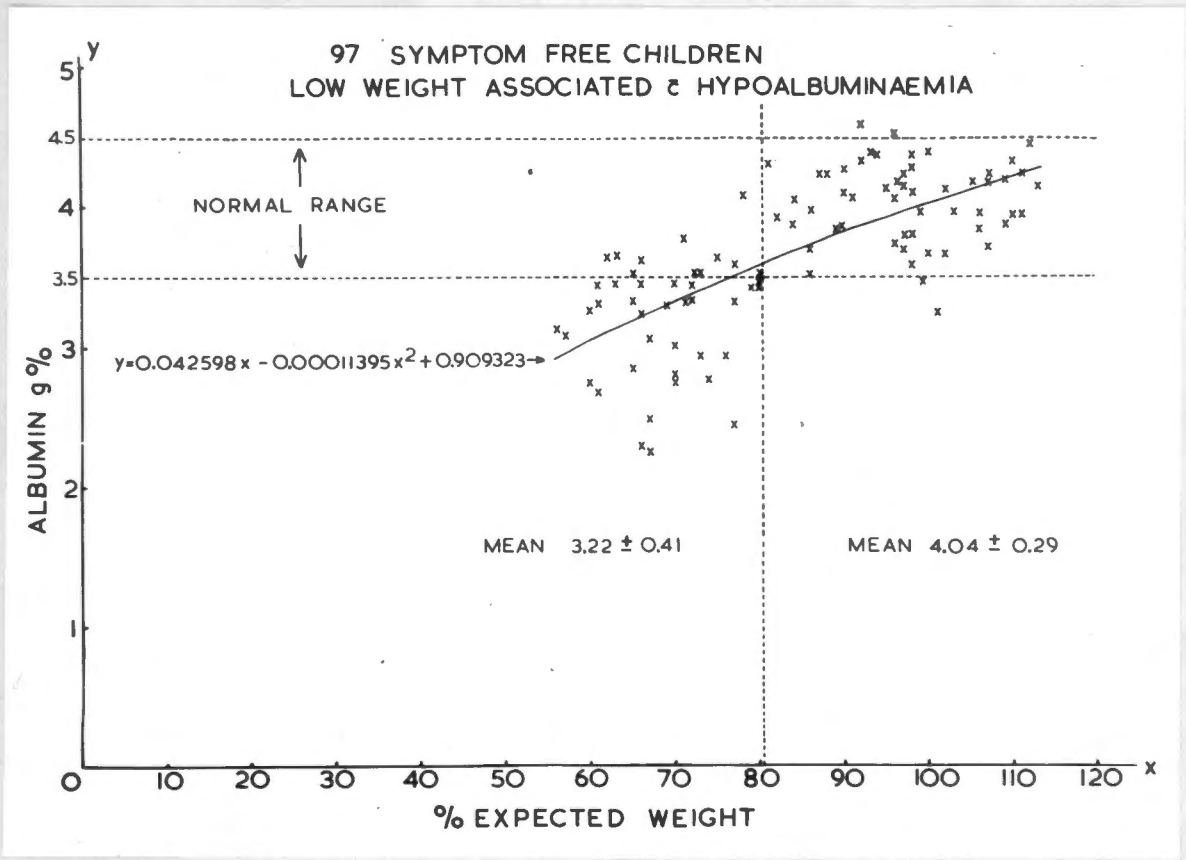


FIGURE. 23.

WEIGHT FOR AGE OF SYMPTOM-FREE CONTROLS.

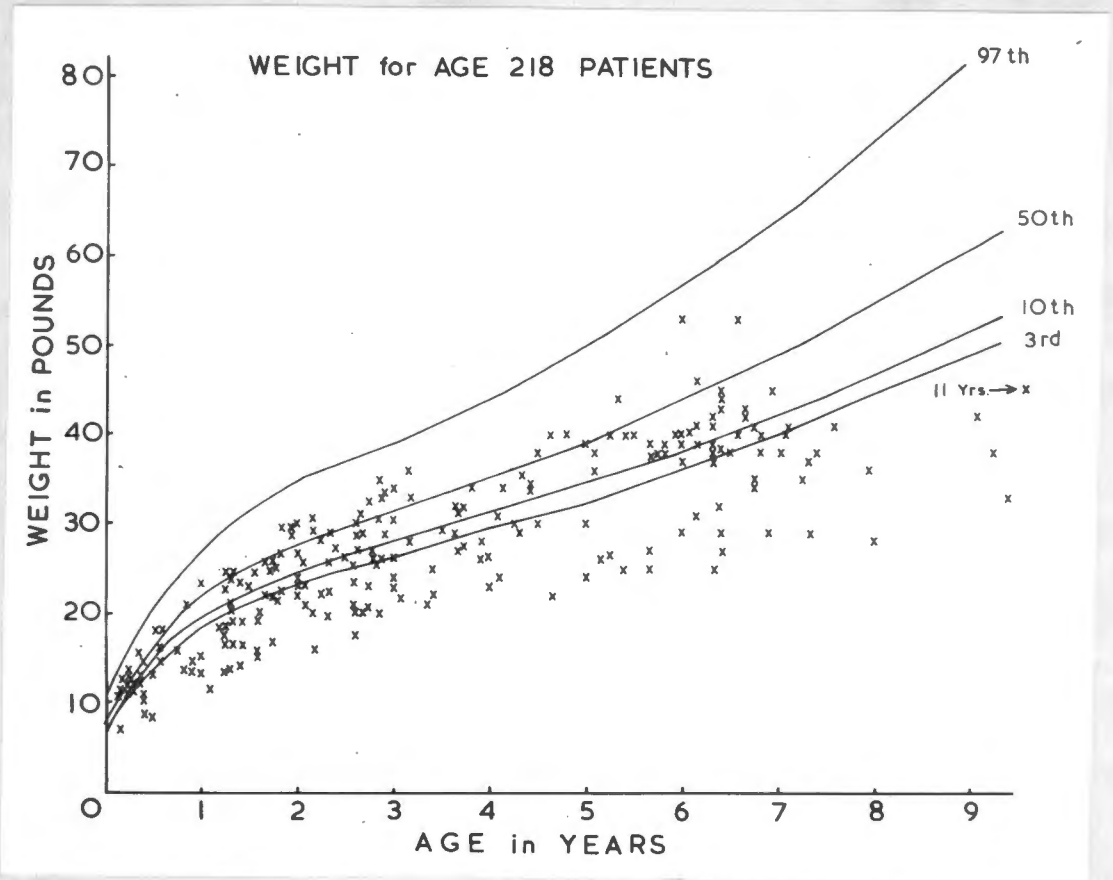
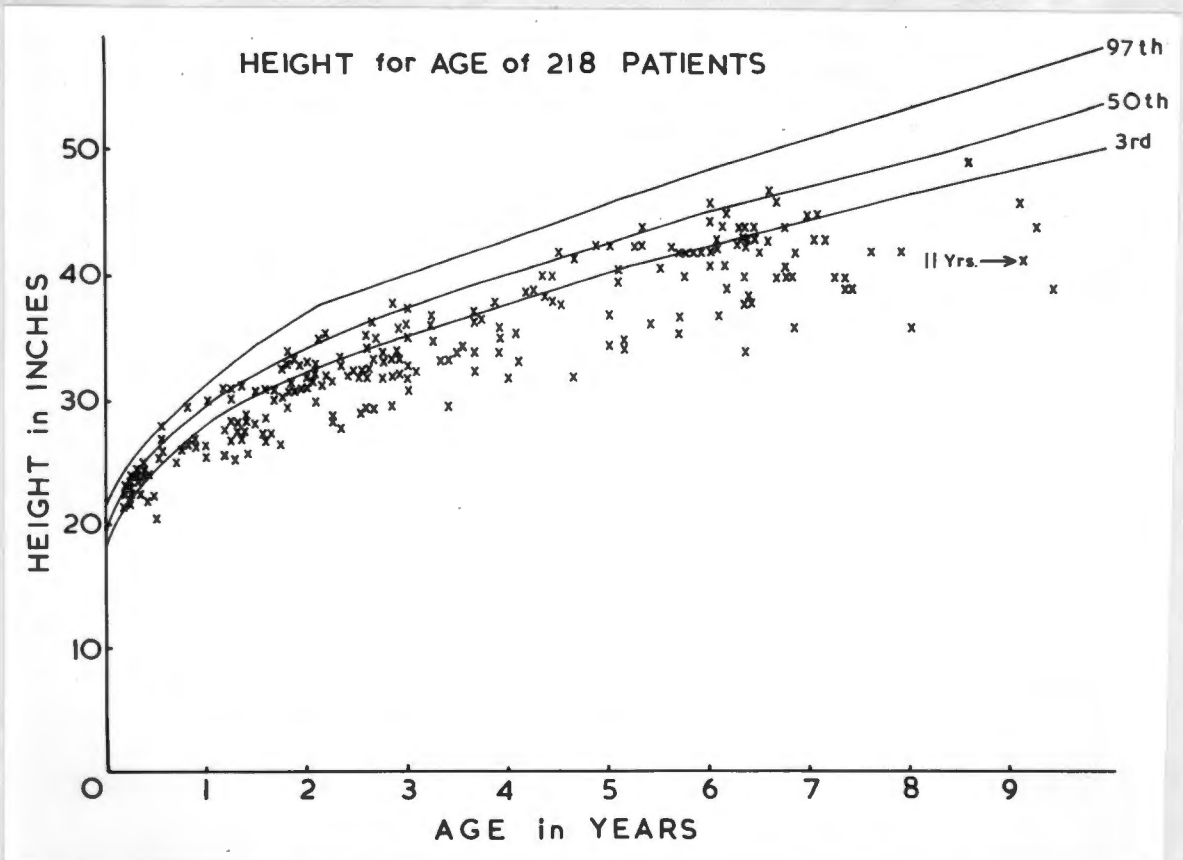



FIGURE.24.

HEIGHT FOR AGE OF SYMPTOM-FREE CONTROLS.



The mean albumin was significantly lower in the low weight patients than in those above 80% of expected weight. In Fig. 22 the serum albumin in g% is plotted against the weight expressed as a percentage of the mean expected weight, for all cases in the 2 groups.

As with the gastro-enteritis subjects there is a striking relationship between increasing weight deficit and hypo-albuminaemia, as indicated by the quadratic regression line fitted to the figures. In this instance however, the quadratic regression did not show the same advantage over a linear regression in that the slope did not flatten out to the same degree after weight became normal, as in the gastro-enteritis study. The correlation between low weight and hypo-albuminaemia to a linear regression ($y= 1.702 + .2325\ x$) was highly significant ($t=.7046$, $p<0.001$). On these data then, the association of low weight for age and hypo-albuminaemia is confirmed in the absence of diarrhoea and acute illness.

Weight and height: For an assessment of the relation between weight and height for age the data of symptom-free children, the post-kwashiorkor patients and their sibling controls were used. The weight and height was known for a total of 218 of such children.

It needs to be pointed out that where children were selected, they were selected by virtue of a given weight for age and were measured for length only after this. The weight/height relation is therefore a random representation as opposed to the weight for age which is not random for the population.

In Figs. 23 and 24 the weight and height of these children are plotted respectively against the Boston normal range.

In weight there were 43% below the normal range and in height 65% were below normal. There are therefore, many more children who are short for their age than low in weight. All the children below the normal weight for age

FIGURE. 25.

WEIGHT ABOVE 90% OF EXPECTED.

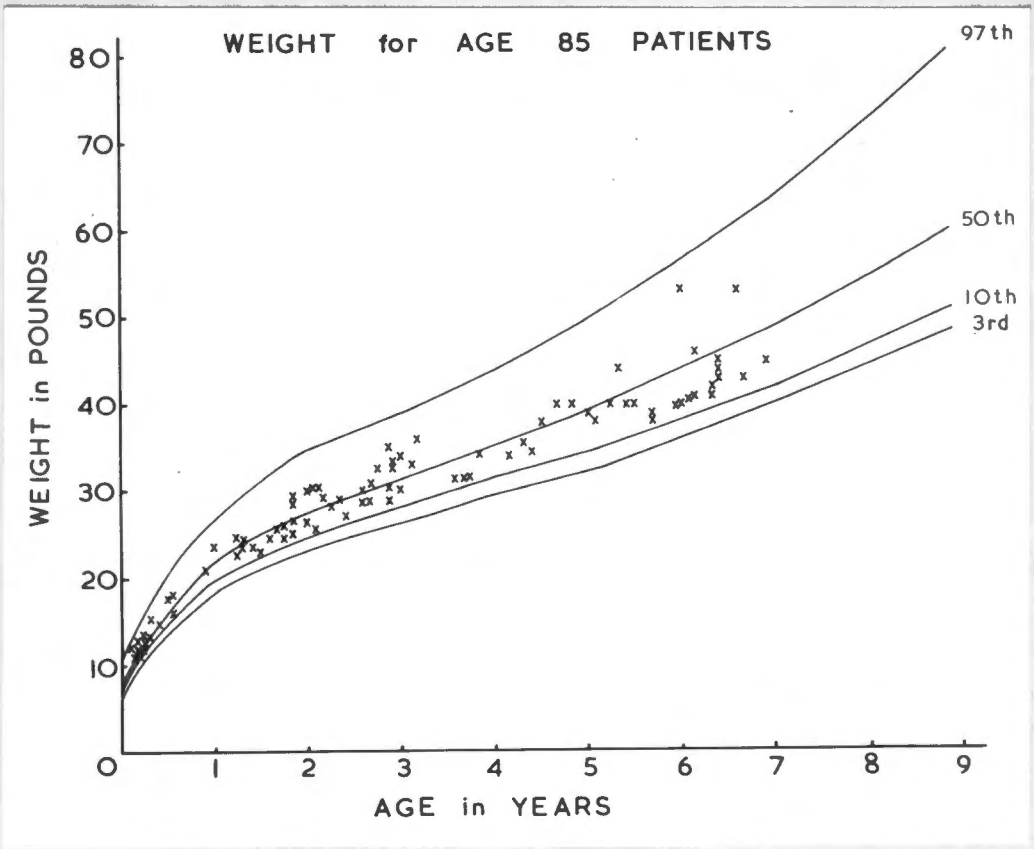



FIGURE. 26

HEIGHT OF "NORMAL" WEIGHT CHILDREN.

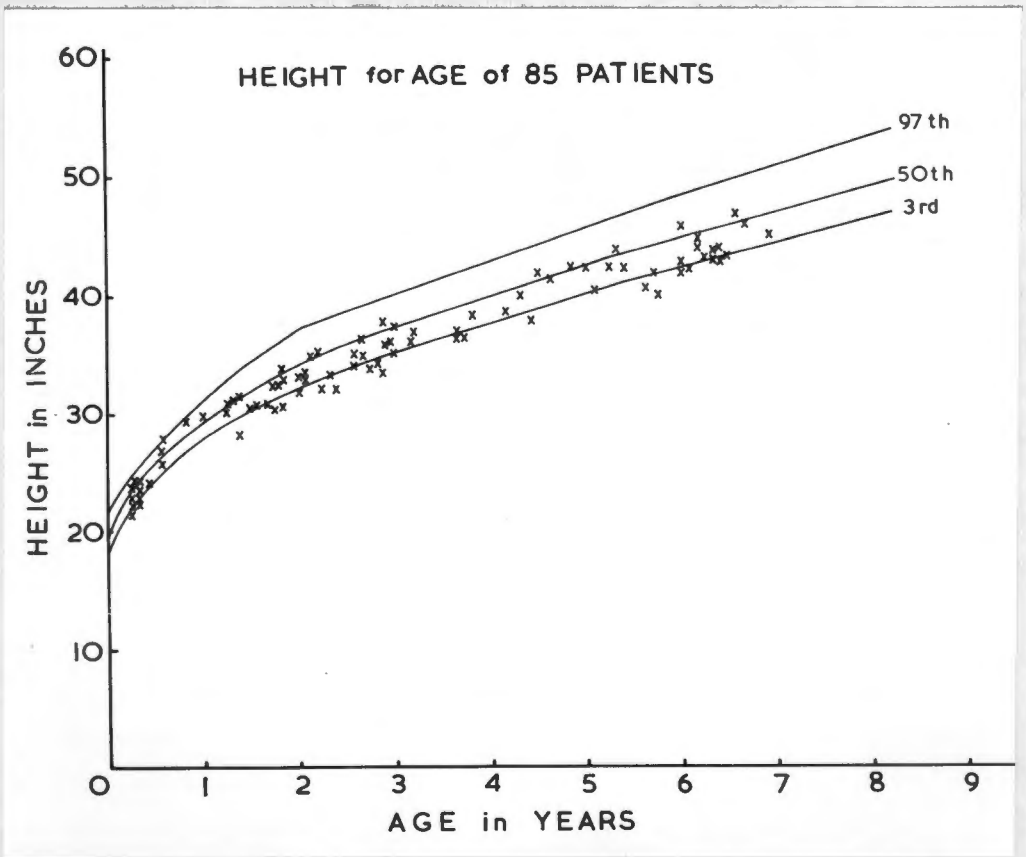


FIGURE. 27.

WEIGHT BELOW 90% OF EXPECTED.

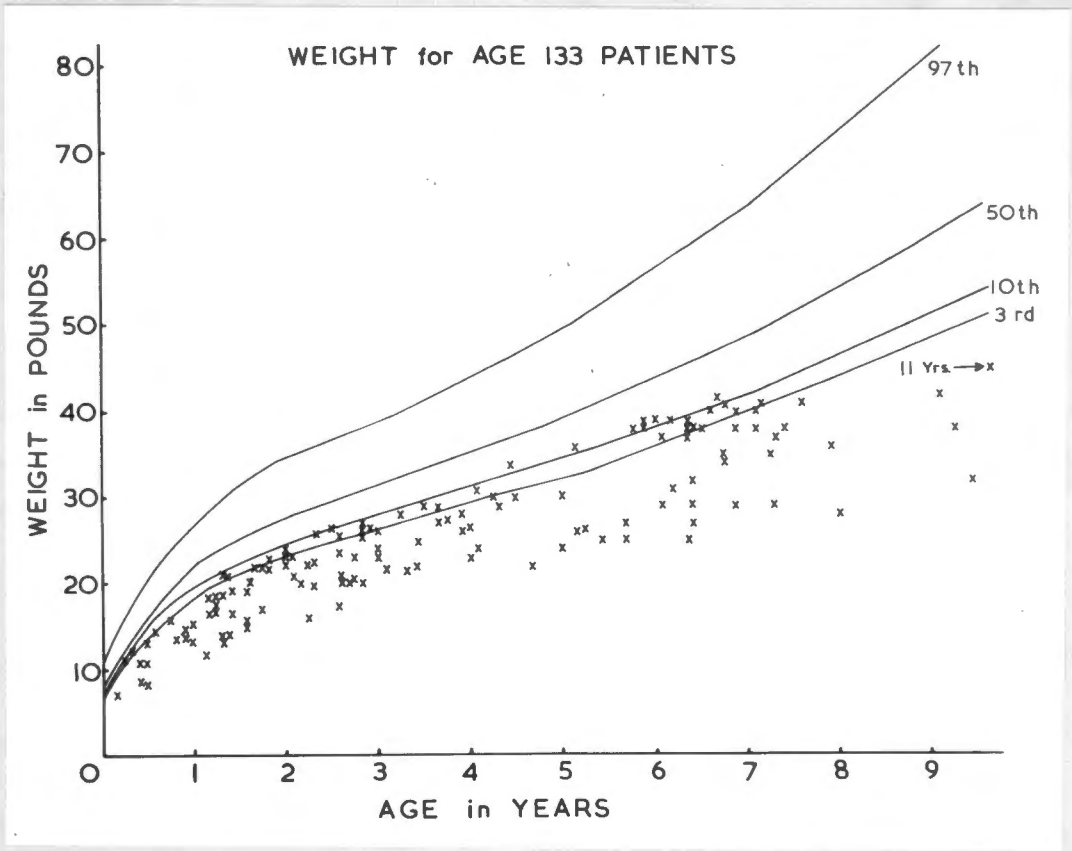
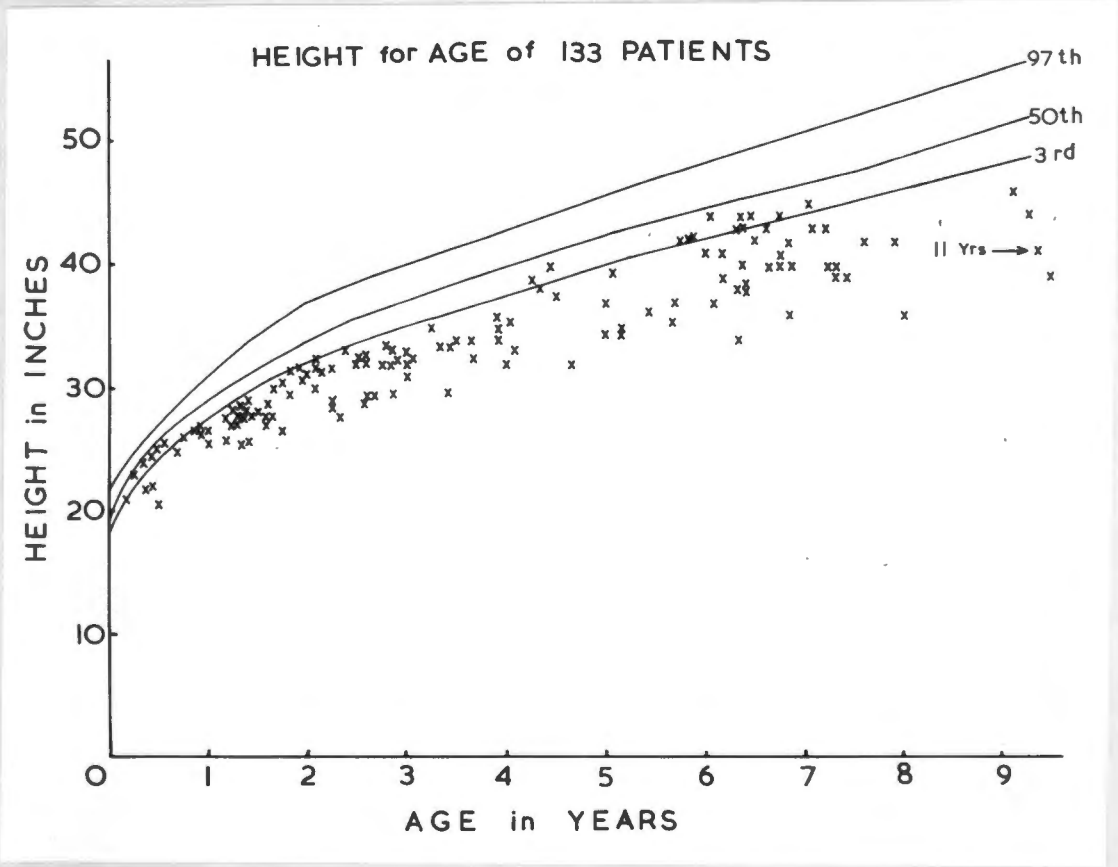



FIGURE. 28.

HEIGHT OF "LOW" WEIGHT CHILDREN.



were also below the normal height.

The majority of children who were above 90% of the expected weight for age were normal in height. The weights of these patients are shown in Fig. 25. In Fig.26 the heights of the same children are indicated. Of these children 24% were below the 3rd percentile in height. Note also that there were more children above the 50th weight percentile than above this height percentile. Those who were below the normal height were almost always very close to the 3rd percentile line.

The majority of children who were below 90% of expected weight were stunted. The weights of these children are shown in Fig.27 and the height in Fig.28. Of the 133 children only 11% were normal in height. Note the gross degree of stunting in many of these children.

The children who are normal in weight therefore may be shorter than their American counterparts. Although the weights tend to be in a higher percentile than the heights, the majority of normal weight children are also within the normal range for height. The low weight children are below the normal range for height.

The height/weight ratios of the two groups of children were compared to the theroretical normal ratio.

The ratios of 78 normal weight children are plotted in Fig.29. A regression line of these is compared with that derived from the normal calculated ratio (50th percentile height and weight). A "t" test on the Null Hypothesis showed that there was not a significant difference between the latter and the observed figures in height/weight ratio ($t=0.012$ $p=< 0.90$). This indicated that the heights of the normal weight children are in proportion to their weights on the American standard.

In Fig. 30 a comparison is drawn between the theoretical normal ratio

FIGURE. 29.

HEIGHT/WEIGHT RATIO OF NORMAL WEIGHT CHILDREN.

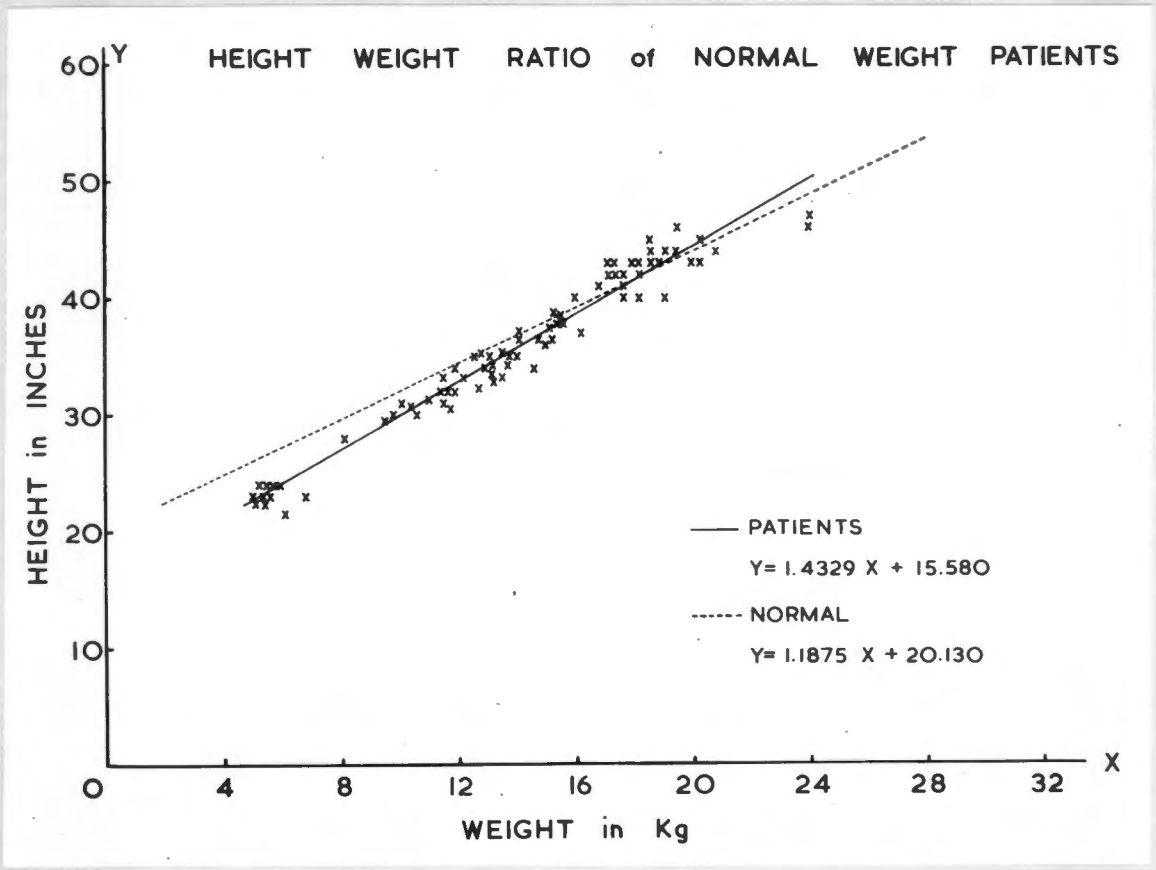
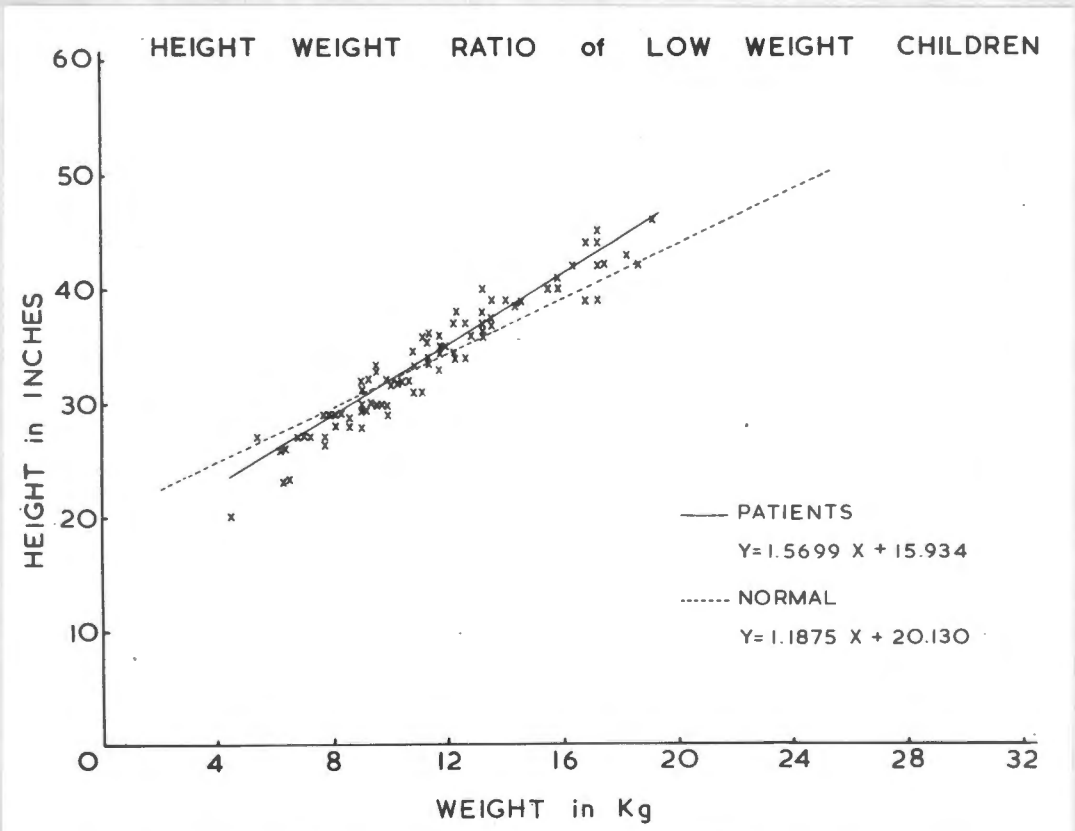



FIGURE. 30.

HEIGHT/WEIGHT RATIO OF LOW WEIGHT CHILDREN.



and the ratio of 84 low weight children. On statistical analysis the height/weight ratio of the low weight children does not differ significantly from the theoretical normal ratio ($t = 0.033$ $p = < 0.90$).

It can therefore be concluded that the children of this study had a proportionate growth failure in weight and height. Their body proportions therefore are those of normal children of a younger age.

The degree of stunting has been calculated in a group of 131 children. These children had a mean expected weight of 84.7% and a mean expected height of 89.4%. The group was divided into two, giving 53 children who were less than 80% of the expected weight and 78 children who were above 80% of the expected weight.

The weight and height of each child was expressed as a percentage of the ideal expected and stunting was calculated in inches below the ideal height for each child.

In Table 29 the age of the patients in each group is indicated.

Table 29.

| | Age in years. | |
|---|---|---|
| | Mean | Range. |
| Below 80% expected weight | 6 | 1 - 9 |
| Above 80% expected weight | 4 | ¼ - 7 |

The normal weight patients were slightly younger than the low weight children and included some very young infants.

In Table 30 the mean figures of height and weight are shown for each group.

Table 30.

Mean values for weight and height.

| | Ideal Height Inches | Actual Height Inches | Stunting Inches | Wt% | Ht% |
|---|---|---|---|---|---|
| <80% Expt.Wt. | 42.9 | 35.7 | 7 | 68 | 83 |
| >80% " " | 37.7 | 35.5 | 2 | 96 | 94 |

Stunting ranged between 1 - 14" and 0 - 6" in the 2 groups respectively.

From the last two columns in the table it appears (falsely) that the children had lost weight out of all proportion to their loss of height. In the normal weight group the two figures are comparable.

Assuming that the mean length at birth is 21", the low weight children have grown 15" since birth instead of an ideal 22" i.e. 67% of the expected growth.

The normal weight children have grown 14.5" instead of 16.7" i.e. 87% of the expected growth.

Expressing the length in this way makes the weight deficit and "growth" deficit much more comparable and is a better indication of the degree of stunting.

It can therefore be concluded that in the absence of acute illness weight and height are proportionally affected in nutritional growth failure.

FIGURE. 31.

FOLLOW-UP WEIGHT OF POST-KWASHIORKOR PATIENTS.

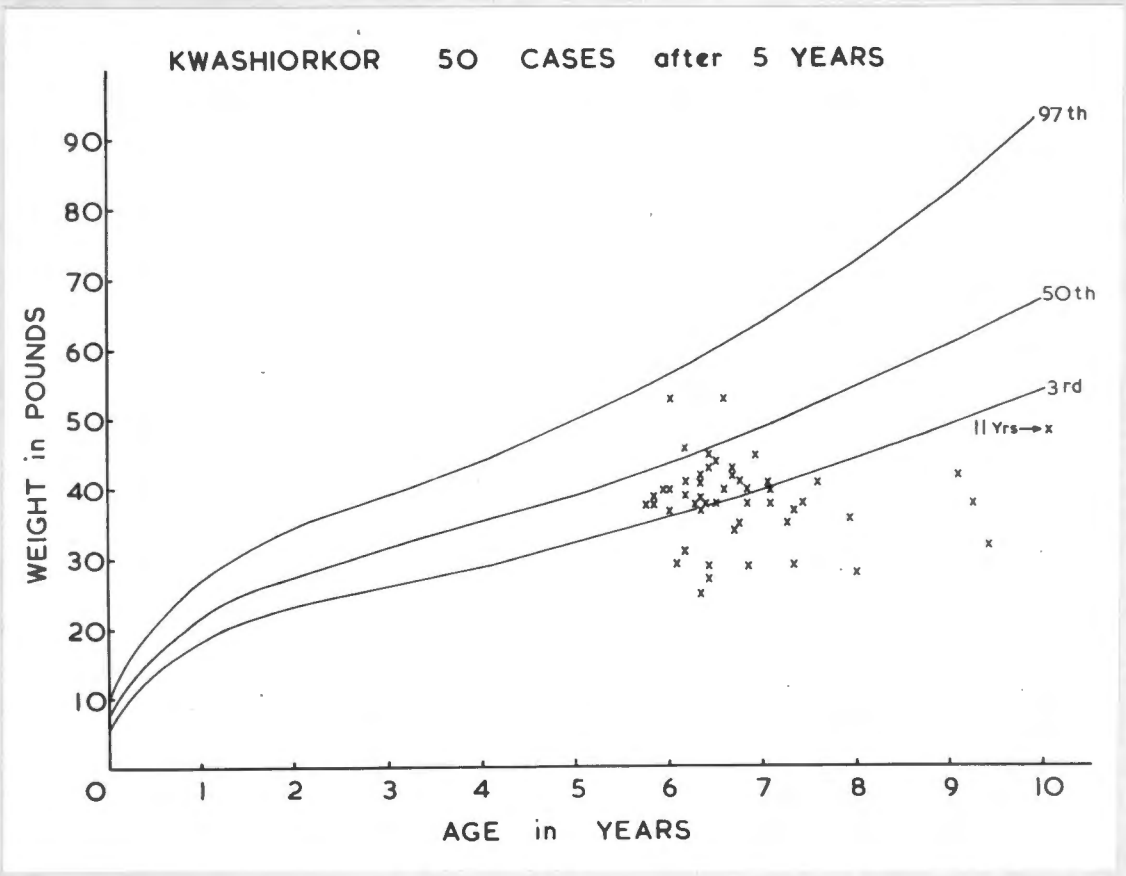



FIGURE. 32.

FOLLOW-UP HEIGHT OF POST-KWASHIORKOR PATIENTS.

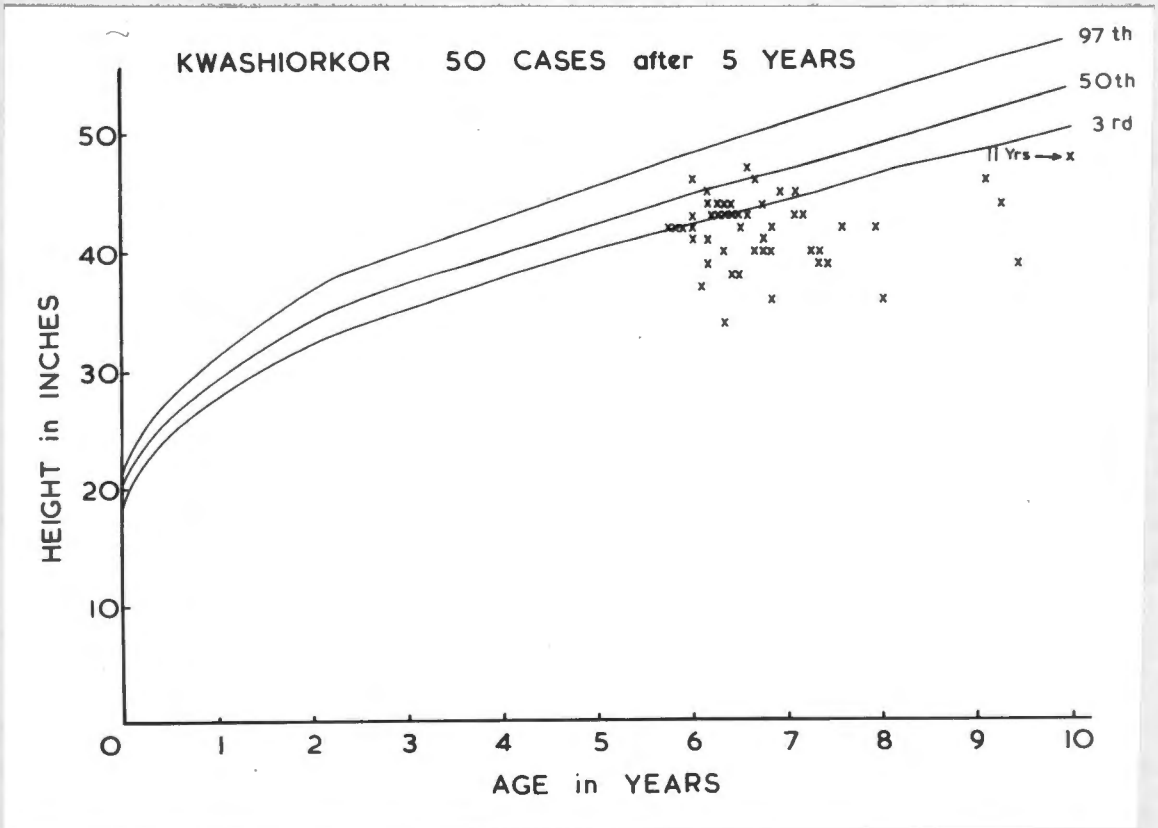


FIGURE. 33.

SERUM ALBUMIN AND WEIGHT OF POST-KWASHIORKOR PATIENTS AT FOLLOW-UP.

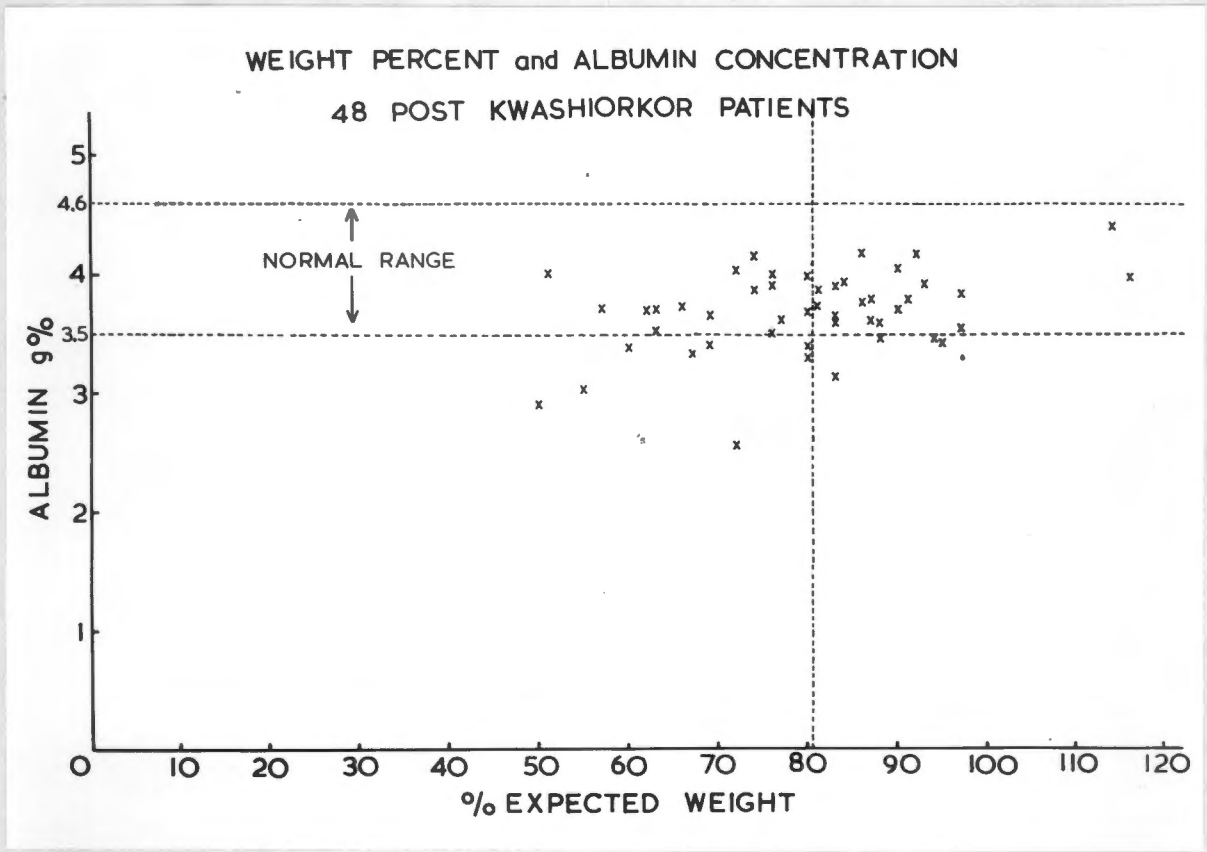


FIGURE. 34.

WEIGHTS OF KWASHIORKOR PATIENTS ON ADMISSION.

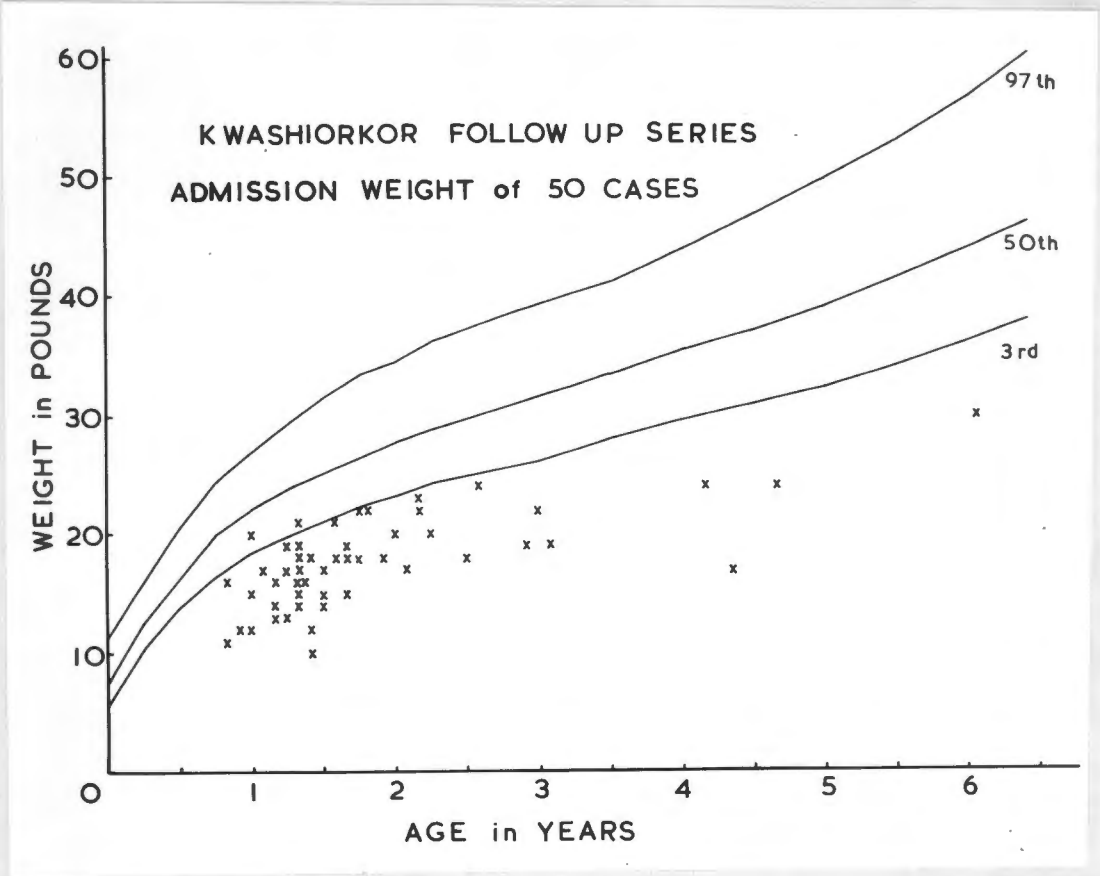



FIGURE. 35.

HEIGHTS OF KWASHIORKOR PATIENTS ON ADMISSION.

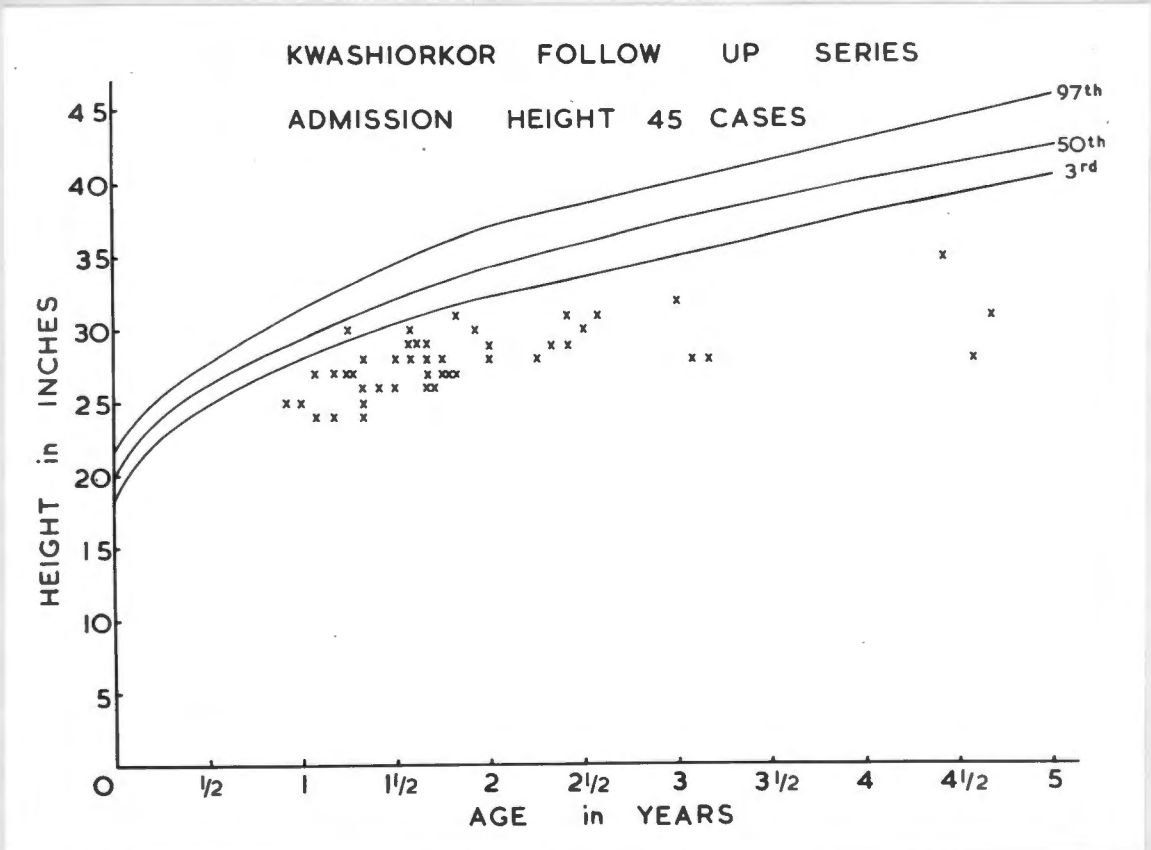


FIGURE. 36.

WEIGHTS OF SIBLINGS ON ADMISSION.

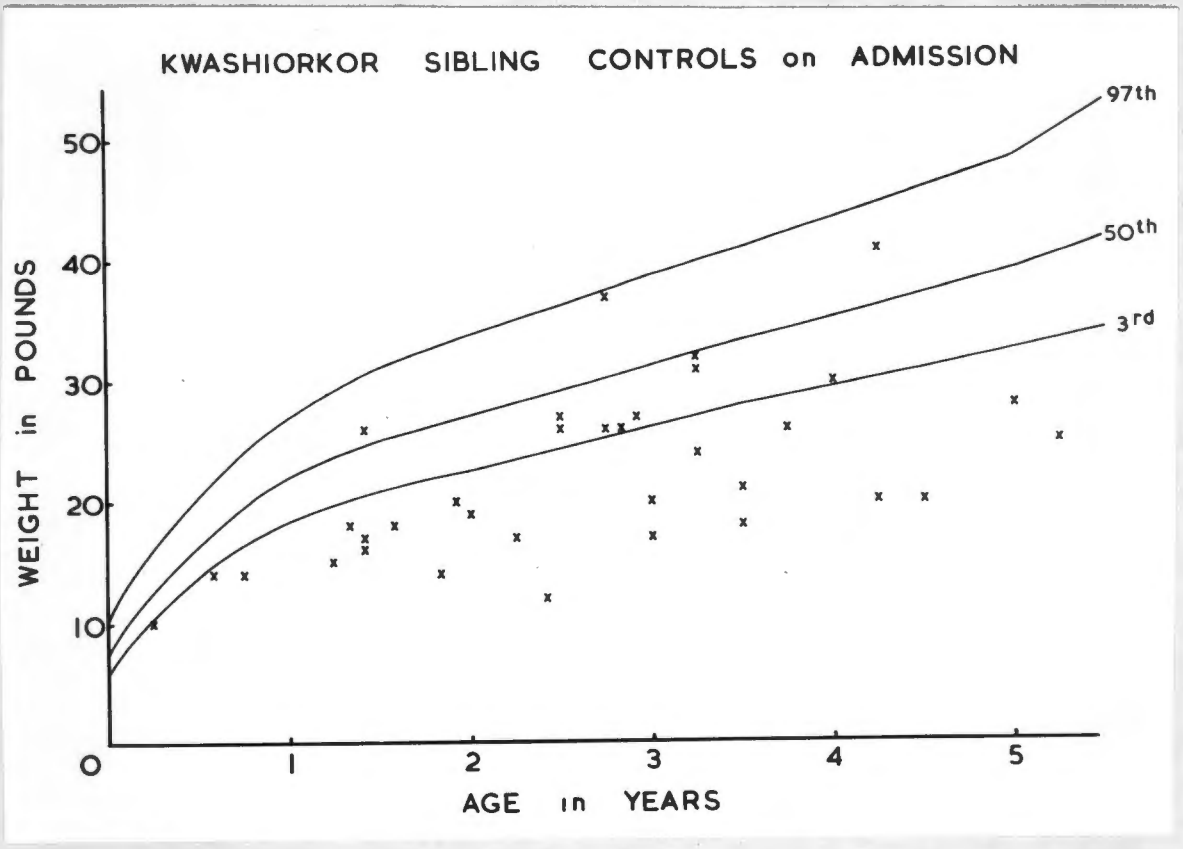



FIGURE. 37.

HEIGHTS OF SIBLINGS ON ADMISSION.

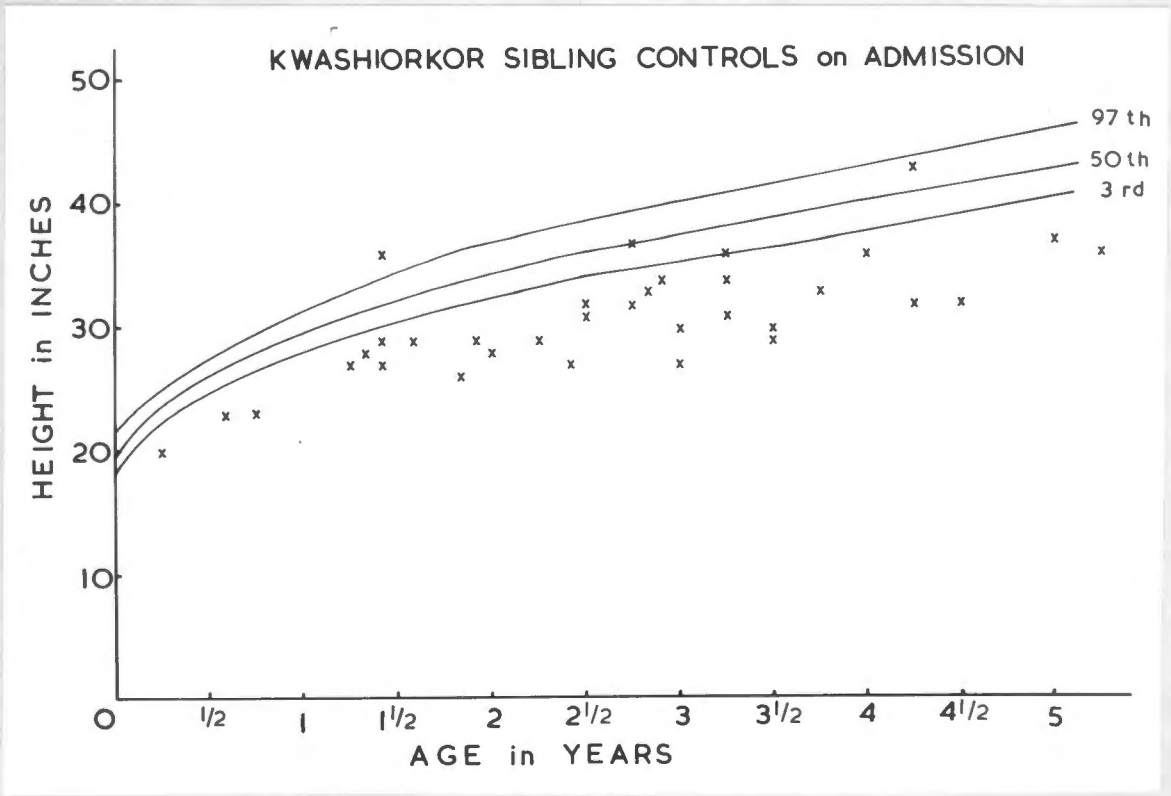


FIGURE. 38.

WEIGHTS OF SIBLINGS AT FOLLOW-UP.

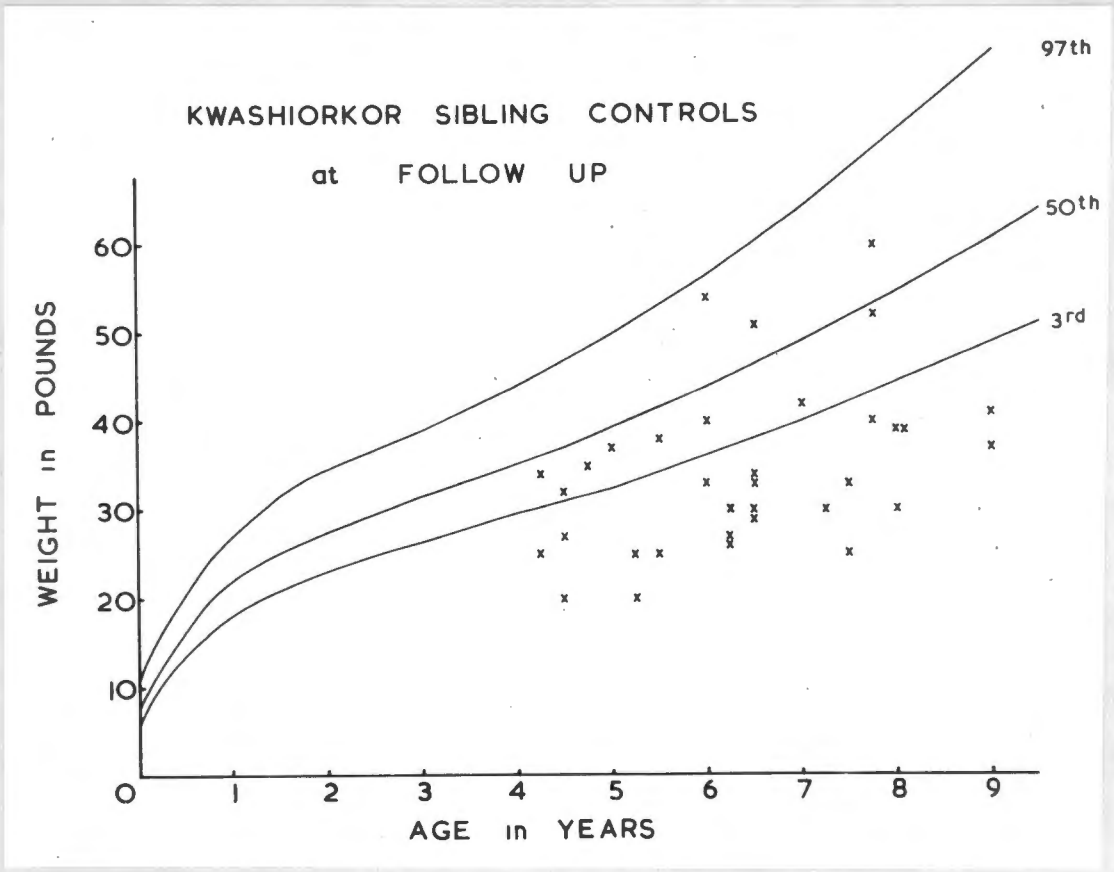
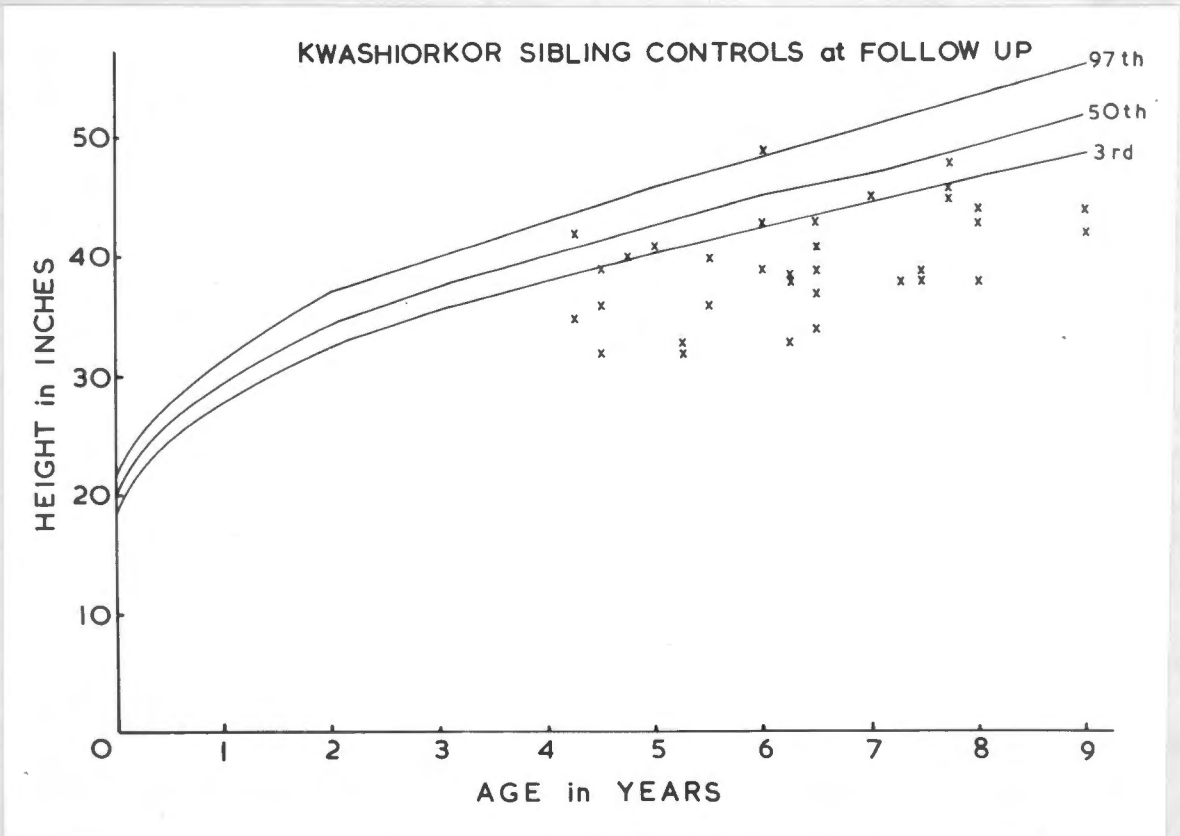



FIGURE. 39.

HEIGHTS OF SIBLINGS AT FOLLOW-UP.



## A GROWTH STUDY IN THE POST-KWASHIORKOR PATIENTS AND THEIR SIBLING CONTROLS.

The follow-up weights and heights of the 50 post-kwashiorkor patients are shown in Figs. 31 and 32. All had been followed for a period of 5 years after the illness. From the graphs it is seen that half the patients are below the normal weight range and 70% of them are below the normal range of height for age.

There were 12 patients with hypo-albuminaemia out of 48 (25%). In 2 patients blood was not obtained. Two of the children with hypo-albuminaemia were above 90% expected weight. These figures are shown in Fig.33. Note that although the serum albumin is within the normal range, the majority are below the normal mean value.

The available weights and heights of these children 5 years ago are shown in Figs.34 and 35. Note here that almost all patients were both underweight and stunted.

During the 5 year period therefore, there were more children who had gained weight into the normal percentile than had reached the normal range for height.

There were 34 siblings on whom weights and heights were available initially and again at follow-up. Here the follow-up period ranged between 3 and 5 years. In Figs. 36 and 37 the initial weights and heights of these children are shown. There were 68% of children below weight and 88% were below the normal height for age. A large proportion of these controls were thus comparable to the kwashiorkor patients in their growth failure. At follow-up the figures for weight and height are shown in Figs. 38 and 39. There were now still 68% below the normal weight range. Two of the original low weight children had gained into the normal weight range and 2 of the normal children had dropped below the percentile range. With regard to the height 80% were still stunted

only 4 of the children having grown into the normal range.

These figures indicate the following:-

1. A large proportion of sibling children who did not have kwashiorkor show growth retardation equal in degree to the kwashiorkor patients.
2. Weight gain is more rapid than gain in height when growth does improve.
3. The majority of kwashiorkor patients failed to "catch up" to normal during the 5 years after their illness but their growth was if anything better than that of their siblings who did not have kwashiorkor.

A study of bone age was also undertaken on the kwashiorkor patients. Bone ages were available on 48 patients at the 5 year follow-up visit. The upper limit of the estimated bone age was regarded as representing the bone age of the patient. There was often a very wide range in the estimation due to the gross retardation of some centres compared to others in the same patient.

Bone age was considered to be retarded if there was a difference of more than 1 year between the chronological age and the highest estimated bone age.

In Fig. 40 the bone age of the patients are plotted against the chronological age with a theoretical line drawn to indicate bone age equal to chronological age. Note how very gross the bone age retardation is especially in the older children.

Table 31.

In Table 31 the mean and range of the chronological age and bone age are given.

| | Age in Years. | |
|---|---|---|
| | Mean | Range |
| Chronological age. | 7 | $5\frac{3}{4}$ - 11 |
| Bone age | 5 | $2\frac{1}{2}$ - $7\frac{1}{2}$ |

FIGURE. 41.

WEIGHT IN RELATION TO BONE AGE.

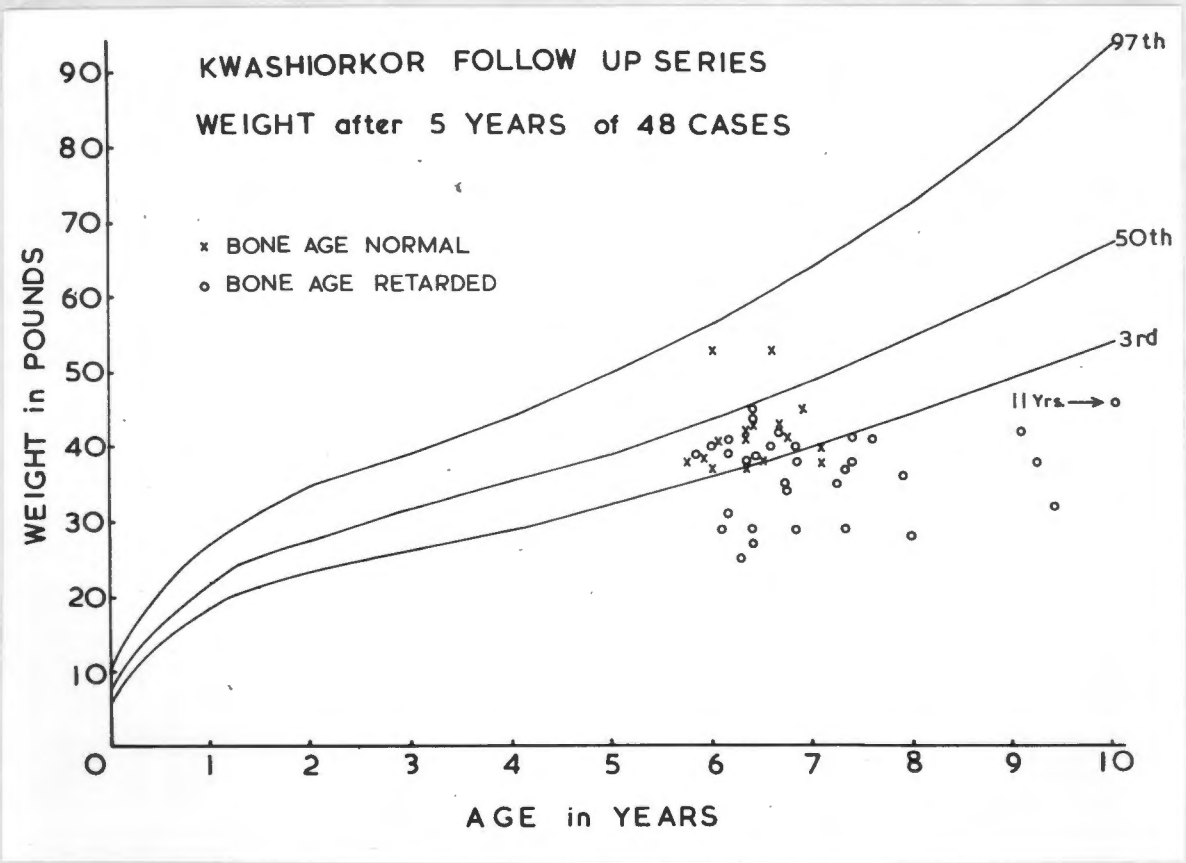
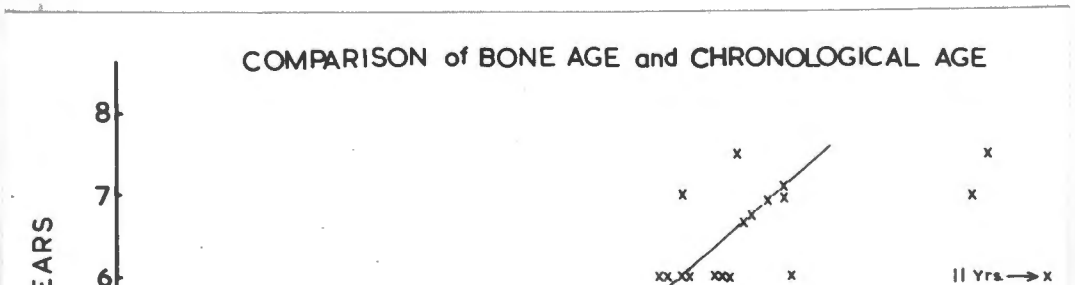



FIGURE. 42.

HEIGHT IN RELATION TO BONE AGE.

FIGURE. 40.

BONE AGE COMPARED WITH CHRONOLOGICAL AGE.



Many of them had a bone age equivalent to the chronological age at which they had the disease. The conclusion is that growth had either ceased since the illness or that changes were present before the disease manifested itself. The latter is more likely because it is known that they did grow in weight and height after the illness.

The weight and height of the patients on whom bone ages were known are shown in Figs. 41 and 42 with an indication of the bone age being normal or retarded.

Of the patients below the normal height there were 5 who had a normal bone age. Of the normal heights only one bone age was retarded.

There were 3 patients at 80% and 1 at 76% of expected weight who had a normal bone age. All the other low weight patients were retarded. There were 11 patients above 80% expected weight with a retarded bone age.

In Table 32 the incidence of retarded bone age is shown against the degree of malnutrition by weight.

Table 32.

Retarded bone age related to the degree of malnutrition in post-kwashiorkor patients.

| | Degree of malnutrition by weight. | | | | |
|---|---|---|---|---|---|
| | 3rd Degree | 2nd Degree | 1st Degree | Normal | Total |
| Total No.patients | 5 | 11 | 22 | 10 | 48 |
| No.Retarded bone age. | 5 | 11 | 9 | 3 | 28 |

Note that all patients who were 2nd and 3rd degree malnourished had a retarded bone age and the incidence dropped in the better weight children. The overall incidence of retarded bone age was 58%. Three patients had a bone age slightly

FIGURE. 43.

WEIGHT PLOTTED AGAINST BONE AGE.

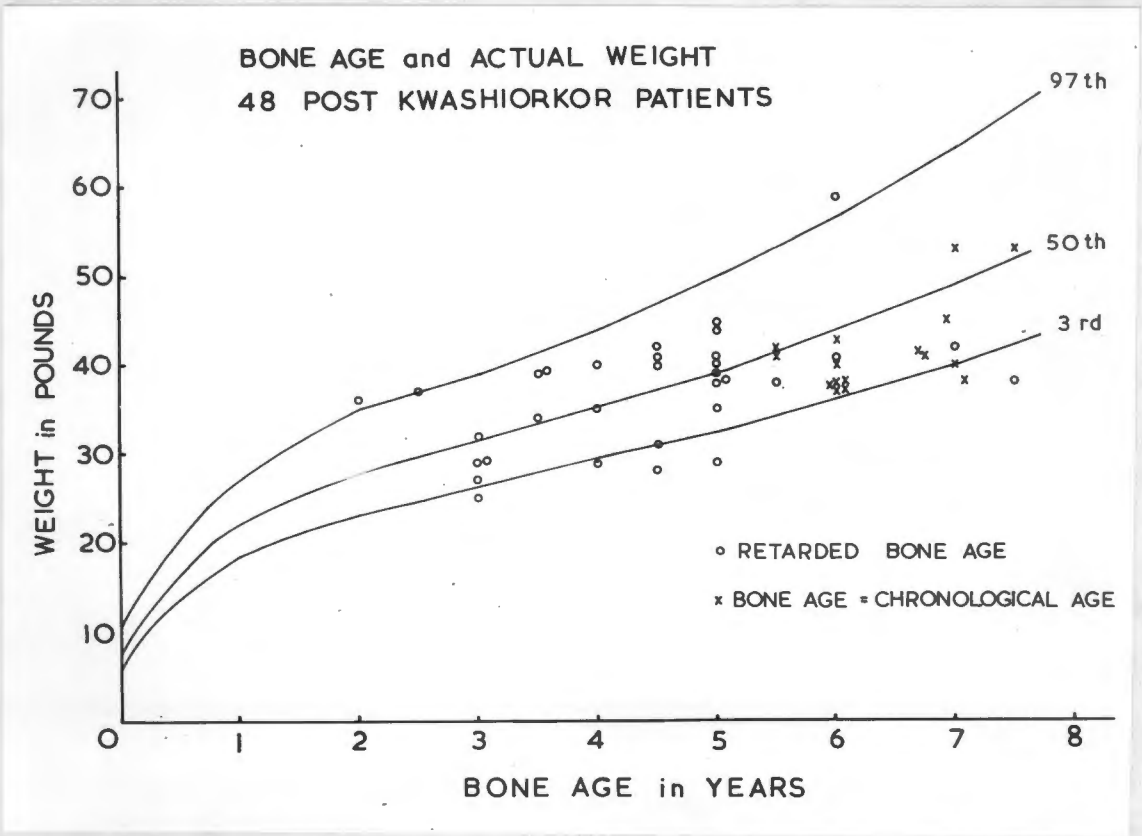
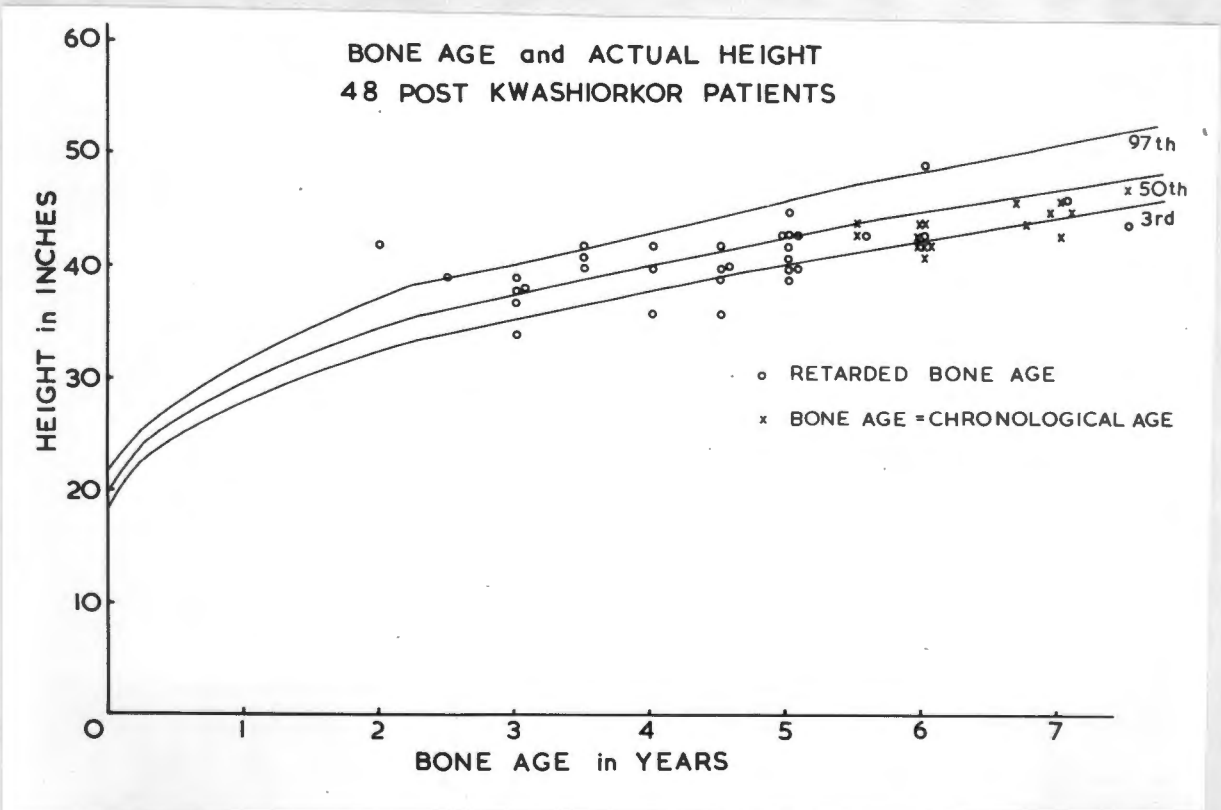



FIGURE. 44.

HEIGHT PLOTTED AGAINST BONE AGE.



in advance of the chronological age.

In Figs.43 and 44 the bone age is substituted for the chronological on the Boston percentile chart for weight and height. Against this the actual weights and heights of the children are plotted. The majority of children seem to be almost perfectly proportioned in weight and height for their bone ages. Some weights and heights are clearly "over-corrected" by the bone age and others remain abnormal in weight and height even when the age is corrected.

From these studies on the kwashiorkor and sibling controls the previous findings of growth failure with reasonably close association between low weight and abnormal height have been confirmed. In addition the kwashiorkor patients show a retardation of bone age which follows the growth failure fairly closely.

It is obvious that this growth failure is not confined to children who had kwasiorkor.

TABLE 33a.

DETAILS OF PATIENTS IN THE DIET TRIAL.

DETAILS OF GASTRO-ENTERITIS DIET TRIAL.

| NAME | DIET | STOOL WEIGHT G/24HRS. 1. | 2. | 3. | 4. | 5. | 6. | 7. | 8. | 9. | 10. | MEAN/ DAY. | STOOL LACTIC ACID G/24HRS. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| E.T. | Casilan | 418 | 330 | 113 | - | - | | | | | | 287 | 0.14 |
| J.W. | " | 701 | 822 | 1074 | 962 | 695 | | | | | | 851 | - |
| O.ME. | " | 330 | 41 | 47 | 48 | 0 | | | | | | 93 | 0.03 |
| F.B. | " | 100 | 83 | 121 | 285 | 309 | | | | | | 180 | 0.03 |
| M.OC. | " | 295 | 314 | 316 | 164 | 117 | | | | | | 241 | 0.01 |
| M.OP | " | 206 | 190 | 73 | 186 | 210 | | | | | | 172 | 0.06 |
| M.H. | " | 140 | 79 | 36 | 30 | 21 | 45 | 36 | 33 | 42 | 89 | 55 | 0.37 |
| M.R. | " | 192 | 85 | 126 | 178 | 110 | 70 | 64 | 29 | 52 | 34 | 94 | 0.09 |
| P.C. | " | 46 | 130 | 68 | 54 | 86 | 122 | 126 | 100 | 87 | 76 | 90 | 0.12 |
| L.K. | " | 229 | 126 | 131 | 139 | 286 | 310 | 198 | 157 | 14 | 60 | 165 | 0.26 |
| L.A. | " | 176 | 87 | 93 | 74 | 3 | 0 | 47 | 105 | 0 | 88 | 67 | 0.01 |
| MA. | " | 400 | 415 | 606 | 723 | 442 | 456 | 908 | 780 | 1168 | 815 | 671 | 0.40 |
| J.F. | " | 235 | 372 | 219 | 282 | 144 | 259 | 553 | 829 | 611 | 690 | 419 | 0.25 |
| K.I. | Milk | 174 | 390 | 100 | 74 | 75 | | | | | | 163 | 0.72 |
| V.M. | " | 599 | 472 | 526 | 595 | 885 | | | | | | 615 | 2.14 |
| J.K. | " | - | - | - | - | - | | | | | | - | - |
| D.P. | " | 490 | 198 | 370 | 210 | 116 | | | | | | 277 | 1.11 |
| V.R. | " | 0 | 270 | 267 | 335 | 224 | | | | | | 219 | 0.38 |
| M.O. | " | 477 | 795 | 587 | 595 | 440 | 442 | 412 | 495 | 521 | 388 | 515 | 4.25 |
| O.M. | " | 228 | 155 | 208 | 168 | 153 | 210 | 235 | 160 | 173 | 199 | 189 | 0.18 |
| D.B. | " | 122 | 362 | 213 | 75 | 110 | 127 | 108 | 80 | 71 | 176 | 144 | 0.82 |
| M.P. | " | 123 | 76 | 39 | 96 | 77 | 165 | 466 | 438 | 872 | 463 | 282 | 0.20 |
| R.P. | " | 131 | 163 | 256 | 213 | 218 | 242 | 154 | 274 | 284 | 212 | 215 | 0.96 |
| S.v.S. | " | 343 | 1058 | 747 | 583 | 825 | 383 | 403 | 533 | 446 | 480 | 580 | 4.50 |
| P.M. | " | 147 | 312 | 512 | 345 | 219 | 201 | 90 | 41 | 132 | 74 | 207 | 2.21 |

TABLE 33b.

DETAILS OF PATIENTS IN THE DIET TRIAL.

DETAILS OF GASTRO-ENTERITIS DIET TRIAL.

| NAME | AGE MONTHS | %EXPT.WT. | ALBUMIN G% | STOOL EXAM. | DIET | DAYS IN HOSPITAL | STOOL WT.G/24 HRS. MEAN/DAY. | STOOL L.A. G/24HRS | COMMENT |
|---|---|---|---|---|---|---|---|---|---|
| E.T. | 11 | 48 | 2.69 | Shigella | Casilan | 5 | 287 | 0.14 | Developed Peritonitis. Died in the 2nd week. |
| J.W. | 17 | 70 | 2.58 | Shigella | " | 5 | 851 | - | Prolonged diarrhoea treated in hospital for several weeks. |
| O.ME. | 9 | 81 | 3.59 | Ascaris | " | 5 | 93 | 0.03 | Discharged day 6. |
| F.B. | 16 | 71 | 2.86 | Yeasts. Ascaris. Trichomonas hominis. | " | 5 | 180 | 0.03 | Discharged day 6. |
| M.OC. | 3 | 94 | 3.68 | Pus | " | 5 | 241 | 0.01 | Discharged day 6. |
| M.OP. | 6 | 51 | 3.03 | Shigella Giardia | " | 5 | 172 | 0.06 | Discharged day 6. |
| M.H. | 2 | 76 | 3.05 | Pus | " | 10 | 55 | 0.37 | Discharged day 12. |
| M.R. | 5 | 71 | 3.05 | Pus Giardia | " | 10 | 94 | 0.09 | Discharged day 11. |
| P.C. | 7 | 91 | 3.50 | Ascaris | " | 10 | 90 | 0.12 | Discharged day 11. |
| L.K. | 8 | 64 | 3.52 | Shigella Giardia | " | 10 | 165 | 0.26 | Diarrhoea recurred after 3 days. |
| L.A. | 16 | 98 | 3.53 | Salmonellae Ascaris | " | 10 | 67 | 0.01 | Discharged day 12. |
| M.A. | 5 | 97 | - | Shigellae | " | 10 | 671 | 0.40 | Prolonged diarrhoea. |
| J.F. | 11 | 53 | - | Trichomonas hominis. | " | 10 | 419 | 0.25 | Prolonged illness. |
| K.I. | 12 | 60 | 3.78 | Negative | Milk | 5 | 163 | 0.72 | Discharged day 7. |
| V.N. | 5 | 61 | 2.86 | Shigella | " | 5 | 615 | 2.14 | Died during 2nd week. |
| J.K. | 9 | 85 | - | Pus | " | - | - | - | Died within 24 hours. Hyperosmolarity. |
| D.P. | 7 | 81 | 4.44 | Pus.Giardia | " | 5 | 277 | 1.11 | Discharged day 7. |
| V.R. | 10 | 66 | 3.33 | Ascaris | " | 5 | 219 | 0.38 | Discharged day 7. |
| M.O. | 14 | 50 | 1.39 | Pus Trichomonas hominis | " | 10 | 515 | 4.25 | Casilan on day 12 with dramatic response. |
| O.M. | 11 | 62 | 2.67 | Negative | " | 10 | 189 | 0.18 | Discharged day 16. |
| D.B. | 5 | 72 | 2.99 | Negative | " | 10 | 144 | 0.82 | Discharged day 16. |
| M.F. | 7 | 105 | 3.37 | Pus | " | 10 | 282 | 0.20 | Casilan given with no improvement. |
| R.P. | 6 | 80 | 3.24 | Pus | " | 10 | 215 | 0.96 | Discharged day 13. |
| S.v.S. | 5 | 97 | - | Negative | " | 10 | 580 | 4.50 | Discharged day 13. |
| P.M. | 15 | 76 | 3.03 | Negative | " | 10 | 207 | 2.21 | Developed U.R.T infection. Discharged day 20. |

L.A. = Lactic acid.

## RESULTS OF THE DIET TRIAL IN SEVERE GASTRO-ENTERITIS.

Results will be discussed in relation to the lactose-free diet and the nitrogen balance data.

Twenty-five children were studied.

One child died before any treatment was started and in one other treatment had to be changed after 2 days.

Of the remaining patients 9 were studied for 5 days only and 14 were studied for a period of 10 days.

Of these 11 were given milk and 12 were given the lactose-free diet.

The details of the patients are given in Tables 33a and 33b.

Nutritional status: The majority of the patients had a low weight for age (68%) and many had hypo-albuminaemia (68%). An albumin below 3.5 g% was considered abnormal (Method C). Hypo-albuminaemia was present in all low weight patients. Two normal weight patients had hypo-albuminaemia.

Infection: Enteral infection was frequently met with. Shigella was isolated in 6 patients and salmonella in 1. Abundant pus cells were found in an additional 7 patients. The patient with salmonella did not have any pus in the stools. Ascaris was present in 5 patients and giardia lamblia in 4. Trichomonas hominis was present in 4 patients. E.coli was not found in any of the patients. The stools were entirely negative in 5 patients.

Mortality: Three patients died, only 1 during the first week. The patient who died on the first day was well nourished and the other 2 were grossly malnourished. All three had shigella in the stools and the 2 malnourished patients also had pneumonia.

Response to the lactose-free diet: In Table 34 some comparisons are shown between patients on milk and on Casilan.

Table 34.

Casilan compared to milk feeds in different groups of patients.

| | Stool wt. G/24 hrs. | | | | |
|---|---|---|---|---|---|
| | Day 1. | 2 - 4 | 5 - 7 | 8 - 10 | Mean/day. |
| All cases (23) | 263 | 294 | 247 | 316 | 264 |
| Casilan (12) | 267 | 243 | 219 | 322 | 223 |
| Milk (11) | 258 | 344 | 274 | 304 | 305 |
| Infection (8) | 234 | 235 | 233 | 309 | 312 |
| No infection (6) | 187 | 326 | 342 | 376 | 234 |
| Infection on Casilan (5) | 227 | 196 | 200 | 231 | 210 |
| Infection on milk (3) | 244 | 313 | 291 | 438 | 334 |
| Low weight Casilan Inf.(3) | 187 | 103 | 127 | 57 | 119 |
| Low weight milk no Inf.(3) | 166 | 261 | 161 | 123 | 178 |

The stool weight of the first day is given separately and then the mean stool weight per day for each subsequent 3 day period is given. In the last column the mean daily stool weight for the entire period is given. The number of patients is small and in none of the groups could significant differences in stool weight be shown.

Firstly the stool weights of all 23 patients are indicated. It can be seen that for the group as a whole, there was no change in stool weight from admission till 10 days, and the mean stool weight was still grossly abnormal over the last 3 day period of collection.

Comparing the 12 patients on Casilan to the 11 on milk, there is an insignificant difference with a slightly lower mean daily stool weight on Casilan.

There were 8 patients with enteral infection and 6 without in the group studied for 10 days. In both groups stool weights increased over the 10 days and mean daily weights were slightly higher in those with infection than in

the others. There were, however, considerable fluctuations from day to day.

In the next group there were 5 patients with infection on Casilan and 3 on milk. The Casilan patients again had slightly lower mean weights but not significantly so. Very little change occurred in the mean stool weights on Casilan but on milk there was an increase towards the end of the period.

In the last column 3 malnourished patients with infection on Casilan are compared with 3 malnourished patients without infection on milk. Again the Casilan showed a better result.

The data in Table 33 show that, as expected, lactic acid was low in the stools of those who were on the lactose-free diet. Glucose was apparently well absorbed. In the patients on milk there were 5 who had more than 1 g. lactic acid/day. These 5 patients had a mean stool weight of 439 g/day. For those who had less than 1 g. lactic acid/day the mean stool weight was 202 g/day. The mean daily lactic acids were 2.84 g. and 0.51 g. respectively. Diarrhoea was thus more severe in the presence of a high lactic acid. Two of the patients with a high lactic acid were wellnourished. Three had enteral infection and 2 did not. One patient who had continued diarrhoea on milk (M.O.) showed a dramatic response to Casilan subsequently. He had a very high stool lactic acid. Another patient (M.F.) with a low lactic acid showed no response when the diet was changed from milk to Casilan.

Conclusion: It appears that diarrhoea was more severe in the patients who had infections and in those with evidence of fermentation diarrhoea. Results in general were slightly better on Casilan than on milk and one patient with a high lactic acid responded dramatically to a lactose-free diet. Lactose-free milk may thus be of value in selected cases but its routine use has no obvious advantages over milk.

There were 20 patients on whom nitrogen balance data were obtained

NITROGEN BALANCE DATA.

| NAME | %EXPT.WT. | DIET | STOOL EXAM. | MEAN STOOL WT. GM/24HRS. | NITROGEN. INTAKE MG/KG/DAY | NITROGEN. RETENTION MG/KG. | NITROGEN. % RETENTION | NITROGEN. % ABSORPTION | LACTIC ACID G/24HRS. |
|---|---|---|---|---|---|---|---|---|---|
| J.W. | 70 | Casilan | Shigellae | 888 | 598 | -64 | - | 38 | |
| F.B. | 71 | " | Yeasts.Ascaris. Trichomonas hominis. | 200 | 753 | 341 | 45 | 81 | |
| M.H. | 76 | " | Pus | 42 | 960 | 417 | 43 | 84 | |
| L.K. | 64 | " | Shigellae. Giardia | 171 | 918 | 276 | 30 | 78 | |
| M.R. | 71 | " | Pus. Giardia | 125 | 1084 | 350 | 32 | 76 | |
| J.F. | 53 | " | Trichomonas hominis. | 254 | 911 | 503 | 55 | 82 | |
| M.OC. | 94 | " | Pus | 228 | 903 | 345 | 38 | 76 | |
| L.A. | 98 | " | Salmonellae Ascaris | 64 | 812 | 188 | 23 | 93 | |
| O.ME. | 81 | " | Ascaris | 34 | 698 | 354 | 51 | 94 | |
| P.C. | 91 | " | Ascaris | 85 | 730 | 280 | 38 | 86 | |
| M.O. | 50 | Milk | Pus.Trichomonas hominis | 604 | 799 | 332 | 42 | 70 | 4.25 |
| V.M. | 61 | " | Shigellae | 620 | 752 | -35 | - | 33 | 2.14 |
| K.I. | 60 | " | Negative | 160 | 752 | 291 | 39 | 85 | 0.72 |
| P.M. | 76 | " | Negative | 347 | 749 | 295 | 39 | 83 | 2.21 |
| D.B. | 72 | " | Negative | 190 | 889 | 486 | 55 | 81 | 0.82 |
| O.M. | 62 | " | Negative | 171 | 780 | 393 | 50 | 86 | 0.18 |
| D.P. | 81 | " | Pus.Giardia Trichomonas hominis | 224 | 624 | 124 | 20 | 77 | 1.11 |
| M.F. | 105 | " | Pus | 72 | 627 | 172 | 27 | 87 | 0.20 |
| R.P. | 80 | " | Pus | 213 | 760 | 243 | 32 | 79 | 0.96 |
| S.v.S. | 97 | " | Negative | 810 | 827 | 113 | 14 | 43 | 4.50 |

= Mean stool weights for the four days during Nitrogen balance only.

TABLE 35.

NITROGEN BALANCE DATA IN THE DIET TRIAL.

during the first 4 days on oral feeding. The findings and relevant data are indicated in Table 35.

In Table 36 the mean intake, retention and absorption figures are shown to compare results in groups of patients.

Table 36.

| | Nitrogen balance results. | | |
|---|---|---|---|
| | Intake mg/kg./day | Retention mg/kg/day | % Absorption. |
| Casilan group (10) | 837 ± 145 | 299 ± 153 | 79 ± 16 |
| Milk group (10) | 756 ± 81 | 241 ± 152 | 72 ± 19 |
| Infection (12) | 799 ± 147 | 224 ± 74 | 73 ± 18 |
| No infection (8) | 792 ± 77 | 339 ± 126 | 80 ± 15 |
| Low weight (12) | 829 ± 128 | 299 ± 178 | 73 ± 18 |
| Normal weight (8) | 748 ± 98 | 227 ± 94 | 79 ± 16 |
| Low weight Inf. (7) | 838 ± 161 | 231 ± 196 | 66 ± 21 |
| Low weight no Inf.(5) | 816 ± 78 | 394 ± 101 | 83 ± 2 |
| Normal weight (8) | 745 ± 121 | 214 ± 84 | 82 ± 15 |

The mean daily nitrogen intake was high and it was slightly higher on Casilan than on milk feeds.

Nitrogen absorption in general was not grossly impaired but the patients on milk had a lower mean absorption than those on Casilan. Two malnourished patients with shigella infection were in negative balance. One wellnourished patient with more than 4 g. lactic acid/day in the stool had an absorption of only 43%.

Nitrogen retention was lowest in the wellnourished patients. It was lower in the malnourished with infection than in those without infection.

Absorption was least in the malnourished patients with infection

(66 ± 21%). The low weight children without infection (83 ± 2%) were comparable to the normal weight children regardless of infection (82 ± 15%). The differences were not significant in any group compared to the other.

Conclusion: The data indicate relatively good nitrogen absorption at high intakes in patients with severe diarrhoea. Absorption is most impaired in malnourished patients with infection. Without infection absorption in the malnourished was comparable to the wellnourished patients. With the small numbers involved differences were not significant.

TABLE 37a.

CLINICAL DETAILS OF STUDY ON ACID SECRETION.

HISTAMINE TEST DETAILS OF PATIENTS.

| NAME | | AGE - YEARS | WEIGHT. KG. | CLINICAL | | | G% HAEMOGLOBIN |
|---|---|---|---|---|---|---|---|
| | | | | SKIN LESIONS | OEDEMA | SEVERITY | |
| M.W. | 1. | 1. 6/12 | 8.3 | Minimal | Moderate | Mild | 9 |
| | 2. | 18 days | 9.1 | | | | |
| N.N. | 1. | 4 | 13.5 | Mild | Gross | Moderate | 9.8 |
| | 2. | 21 days | 15.8 | | | | |
| I.M. | 1. | 1. 3/12 | 7.4 | Nil | Gross | Moderate | 8.5 |
| | 2. | 20days | 7.8 | | | | |
| E.C. | 1. | 1. 2/12 | 8.8 | Mild | Gross | Moderate | 7.5 |
| | 2. | 28 days | 8.2 | | | | |
| B.M. | 1. | 1. 1/12 | 11.0 | Mild | Slight | Mild | 8.25 |
| | 2. | 20 days | 11.7 | | | | |
| T.W. | 1. | 8/12 | 6.9 | Extensive | Moderate | Moderate | 8.2 |
| | 2. | 14 days | 7.1 | | | | |
| M.V. | 1. | 1. 10/12 | 6.0 | Moderate | Moderate | Moderate | 7.8 |
| | 2. | 14 days | 7.9 | | | | |
| M.A. | 1. | 1. 3/12 | 7.0 | Extensive | Moderate | Severe | 8.6 |
| | 2. | 10 days | 7.9 | | | | |
| J.T. | 1. | 2. 11/12 | 6.8 | Minimal | Gross | Moderate | 8.5 |
| | 2. | 20 days | 7.0 | | | | |
| V.M. | 1. | 1. 5/12 | 9.6 | Minimal | Gross | Moderate | 8.15 |
| | 2. | 40 days | 9.8 | | | | |
| D.L. | 1. | 4 | 9.1 | Extensive | Gross | Severe | 8.2 |
| | 2. | 10 days | 11.7 | | | | |
| L.B. | 1. | 1. 9/12 | 9.9 | Mild | Gross | Mild | 10.4 |
| | 2. | 17 days | 9.9 | | | | |
| G.D. | 1. | 2. 11/12 | 11.8 | Moderate | Moderate | Moderate | 8.9 |
| | 2. | 1 year | 12.9 | | | | |
| G.S. | 1. | 1. 1/12 | 7.1 | Nil | Moderate | Moderate | 10.0 |
| | 2. | 18 days | 7.9 | | | | |
| J.S. | 1. | 1 year | 7.8 | Moderate | Gross | Severe | 9.0 |
| | 2. | 17 days | 7.7 | | | | |
| J.L. | 1. | 1. 1/12 | 5.0 | Minimal | Moderate | Moderate | 8.0 |
| | 2. | 14 days | 5.9 | | | | |
| D.H. | 1. | 6/12 | 5.8 | Mild | Gross | Moderate | 8.5. |
| | 2. | 1 month | 6.2 | | | | |
| L.v.R | 1. | 1. 11/12 | 11.2 | Nil | Moderate | Mild | 6 |
| | 2. | 8 months | 13.3 | | | | |
| D.F. | 1. | 1. 4/12 | 5.8 | Minimal | Slight | Mild | 8 |
| | 2. | 8 months | 8.3 | | | | |
| N.D. | 1. | 1. 1/12 | 7.9 | Extensive | Slight | Severe | 7.5 |
| | 2. | 8 months | 9.4 | | | | |

TABLE 37b.

## DETAILS OF HISTAMINE TEST RESULTS.

### HISTAMINE TEST DETAILS OF PATIENTS.

| NAME | FLUID VOLUME ML/HR. | | | LOWEST pH UNITS | | | TOTAL ACID M.EQ/L. | | | FREE ACID M.EQ/HR. | | | TOTAL ACID M.EQ/HR. | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | F | B | H | F | B | H | F | B | H | F | B | H | F | B | H |
| M.W. 1. | 24 | 34 | 41 | 7.12 | 7.18 | 2.53 | - | - | 46 | - | - | .53 | - | - | 1.01 |
| 2. | 19 | 28 | 50 | 6.92 | 4.55 | 2.11 | 12.8 | 20 | 28 | - | - | .55 | .20 | .36 | .83 |
| N.N. 1. | 17 | 21 | 27 | 5.71 | 7.00 | 2.54 | 12 | - | 36 | - | - | .11 | .06 | - | .84 |
| 2. | 50 | 46 | 68 | 6.52 | 4.39 | 2.15 | 8 | 10 | 42 | - | .11 | 1.37 | .30 | .42 | 3.16 |
| I.M. 1. | 7 | 10 | 25 | 1.88 | 7.99 | 1.40 | 37 | - | 77 | .16 | - | .72 | .26 | - | 1.45 |
| 2. | 27 | 39 | 64 | 6.22 | 3.00 | 2.38 | 4 | 16 | 28 | - | .13 | .35 | .11 | .49 | 1.40 |
| E.C. 1. | 18 | 19 | 28 | 1.92 | 1.90 | 1.52 | 28 | 36 | 60 | .41 | .33 | .47 | .50 | .63 | 1.31 |
| 2. | 40 | 34 | 60 | 2.19 | 1.90 | 2.10 | 28 | 36 | 36 | .56 | .55 | .54 | 1.12 | 1.19 | 1.29 |
| B.M. 1. | 32 | 52 | 71 | 6.58 | 7.06 | 2.72 | 4 | 3 | 27 | - | - | .22 | .13 | .15 | 1.18 |
| 2. | 39 | 40 | 59 | 6.19 | 6.92 | 4.65 | - | - | - | - | - | - | - | - | - |
| T.W. 1. | 13 | 19 | 36 | 2.29 | 1.75 | 1.52 | 42 | 80 | 90 | .21 | .50 | 1.85 | .55 | 1.08 | 3.06 |
| 2. | 10 | 45 | 43 | 6.68 | 1.92 | 1.86 | 14 | 30 | 112 | - | .72 | 1.35 | .14 | 1.17 | 3.91 |
| M.V. 1. | 10 | 37 | 49 | 1.69 | 1.52 | 1.70 | 42 | 70 | 122 | .26 | 1.53 | 2.45 | .42 | 2.27 | 4.41 |
| 2. | 8 | 25 | 31 | 4.68 | 2.39 | 1.02 | 14 | 28 | 104 | - | .14 | 1.75 | .11 | .55 | 2.22 |
| M.A. 1. | 26 | 31 | 53 | 3.98 | 6.80 | 2.12 | - | - | 38 | - | - | .51 | - | - | 1.22 |
| 2. | 34 | 55 | 68 | 6.51 | 7.50 | 3.96 | - | - | 26 | - | - | .54 | - | - | 1.17 |
| J.T 1. | 9 | 18 | 37 | 4.29 | 5.13 | 1.89 | 8 | 10 | 70 | - | - | .65 | .07 | .14 | 2.25 |
| 2. | 20 | 43 | 55 | 2.10 | 2.10 | 2.08 | 50 | 64 | 52 | .56 | .70 | .95 | 1.00 | 2.10 | 2.37 |
| V.M. 1. | 10 | 18 | 28 | 5.40 | 3.40 | 2.35 | 18 | 38 | 56 | - | .05 | .39 | .18 | .47 | 1.22 |
| 2. | 13 | 27 | 72 | 7.12 | 7.42 | 1.41 | 4 | 4 | 80 | - | - | 2.85 | .04 | .09 | 4.00 |
| D.L. 1. | 22 | 14 | 42 | 6.42 | 2.40 | 1.22 | 6 | 23 | 106 | - | .13 | 2.08 | .13 | .25 | 2.00 |
| 2. | 7 | 12 | 28 | 7.06 | 8.33 | 2.82 | 10 | 8 | 70 | - | - | .21 | .07 | .10 | 1.19 |
| L.B. 1. | 2 | 9 | 48 | 6.19 | 1.98 | 1.40 | 4 | 34 | 66 | - | .08 | 1.95 | .01 | .22 | 2.76 |
| 2. | 15 | 7 | 44 | 7.99 | 8.29 | 1.93 | - | - | 32 | - | - | .57 | - | - | 1.45 |
| G.D. 1. | 11 | 20 | 37 | 5.31 | 5.12 | 4.39 | 12 | 10 | 8 | - | - | - | .13 | .20 | .20 |
| 2. | 12 | 11 | 23 | 7.08 | 7.76 | 1.59 | - | - | 29 | - | - | .10 | - | - | .34 |
| G.S. 1. | 10 | 12 | 27 | 2.71 | 5.75 | 1.98 | 20 | 8 | 42 | .06 | - | .45 | .20 | .10 | 1.01 |
| 2. | 28 | 26 | 49 | 2.97 | 2.40 | 1.48 | 36 | 26 | 72 | .39 | .42 | 1.81 | .50 | .68 | 2.88 |
| J.S. 1. | 2 | 7 | 6 | 2.12 | 2.69 | 1.63 | 20 | 55 | 120 | .01 | .02 | .20 | .04 | .12 | .51 |
| 2. | 11 | 35 | 69 | 3.08 | 4.30 | 1.51 | 18 | 14 | 62 | .04 | .05 | 2.00 | .20 | .47 | 3.03 |
| J.L. 1. | 10 | 26 | 36 | 8.12 | 7.68 | 2.09 | - | - | 36 | - | - | .37 | - | - | .88 |
| 2. | 6 | 16 | 23 | 8.67 | 8.15 | 3.10 | - | - | 30 | - | - | .14 | - | - | .49 |
| D.H. 1. | 14 | 6 | 20 | 6.21 | 7.31 | 6.71 | - | - | - | - | - | - | - | - | - |
| 2. | 16 | 22 | 28 | 2.23 | 1.50 | 1.39 | 28 | 54 | 115 | .19 | .26 | 1.37 | .45 | .99 | 2.23 |
| L.v.R.1. | 31 | 68 | 72 | 7.08 | 7.32 | 7.12 | - | - | - | - | - | - | - | - | - |
| 2. | 32 | 20 | 34 | 6.68 | 7.38 | 3.96 | - | - | 14 | - | - | - | - | - | .42 |
| D.P. 1. | 57 | 33 | 21 | 7.51 | 7.51 | 8.25 | - | - | - | - | - | - | - | - | - |
| 2. | 7 | 30 | 40 | 2.96 | 4.58 | 1.97 | 28 | 12 | 40 | .04 | - | .46 | .20 | .30 | 1.14 |
| N.D. 1. | 11 | 13 | 27 | 7.28 | 7.69 | 7.40 | - | - | - | - | - | - | - | - | - |
| 2. | 6 | 10 | 44 | 4.49 | 7.20 | 2.32 | - | - | 32 | - | - | .43 | - | - | .91 |

## GASTRIC SECRETION IN KWASHIORKOR.

In 20 patients the tests were done on admission and recovery.

Difficulties encountered:-

1. It is impossible to do the test in an unco-operative child and it soon became apparent that sedation would facilitate intubation and enhance the subsequent procedure. Intramuscular paraldehyde was considered safe, effective and unlikely to interfere with acid secretion. Anthisan provided a further sedative effect during the latter stages of the test.
2. Aspiration of saliva from the mouth was technically difficult and manipulation increased its secretion. Attempts at separating saliva were thus abandoned. Salivation on the whole was not a problem if the patient was not disturbed.
3. Adequate aspiration of gastric juice was not always achieved although results improved with increasing experience. This is demonstrated in patient J.S. in Table 37 who has a high acid concentration but a low volume and therefore a low total acid output.
4. Minimal bleeding was frequently encountered. Its occurrence was reduced with increasing technical skill and mild suctioning.
5. Abundant mucus was often present in the aspirated gastric juice making titration difficult especially if blood staining was present.
6. A maximum histamine dose response has not been established in infants. For these tests 8 body weight doses were used (0.08 mg/kg) to ensure adequate absorption in the presence of oedema.

No untoward effects were noticed from the histamine. Some cases had mild flushing and a transient tachycardia.

No control subjects were studied.

FIGURE. 45.

20 PATIENTS VOLUME OF FLUID.

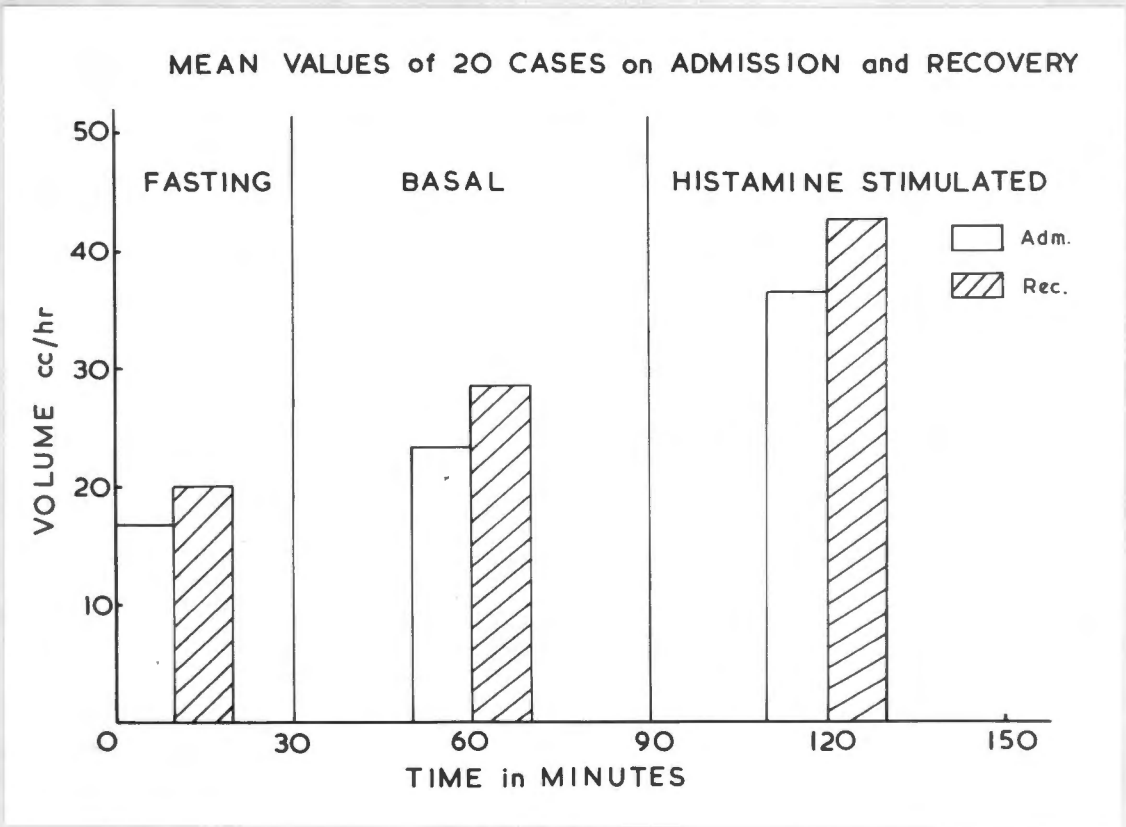



FIGURE. 46.

20 PATIENTS LOWEST pH.

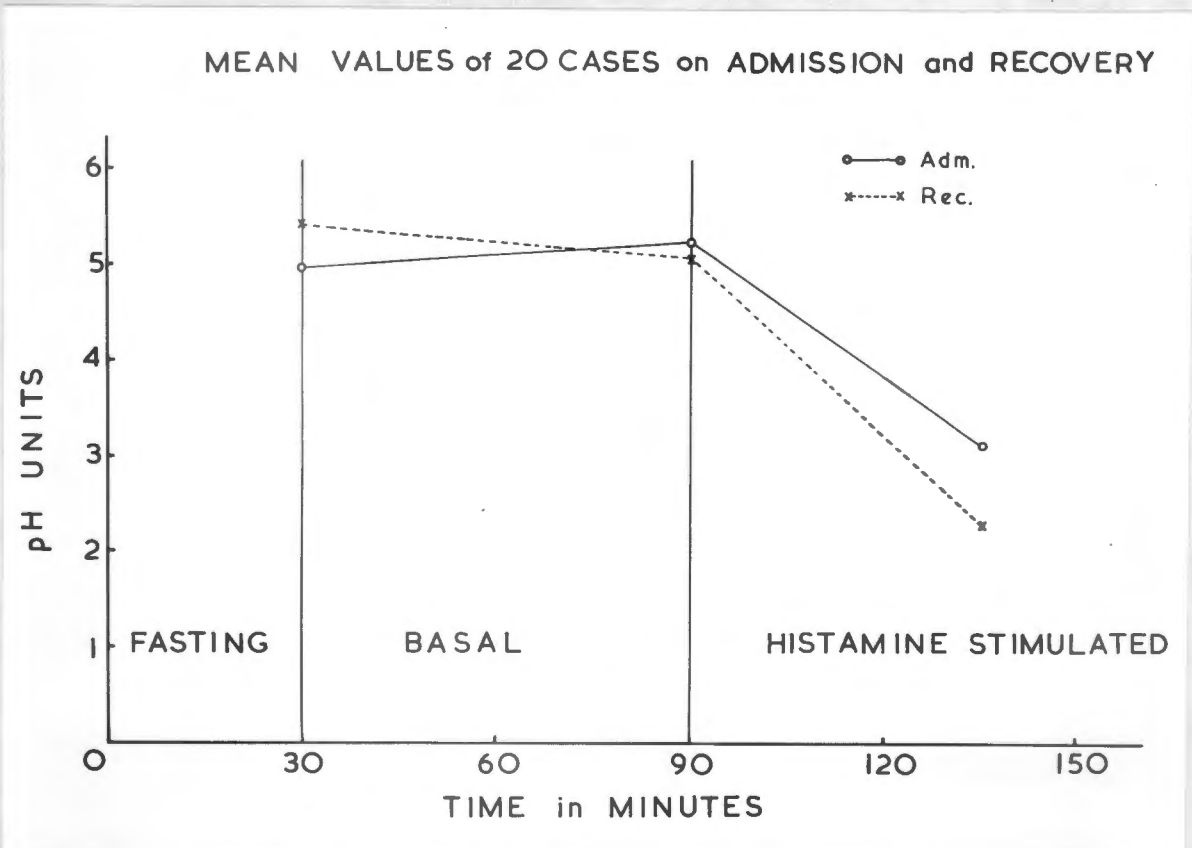


FIGURE. 47.

20 PATIENTS HIGHEST ACID CONCENTRATION.

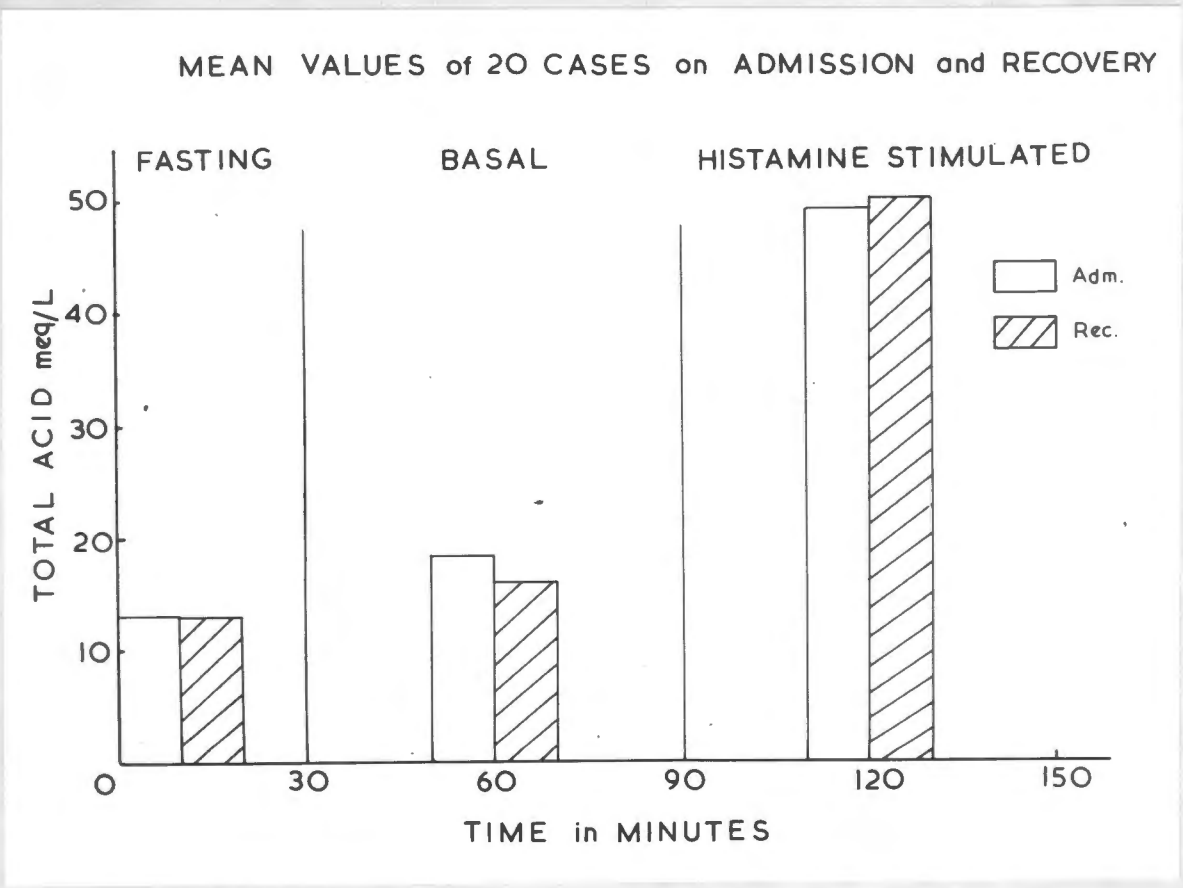



FIGURE. 48.

20 PATIENTS TOTAL ACID OUTPUT.

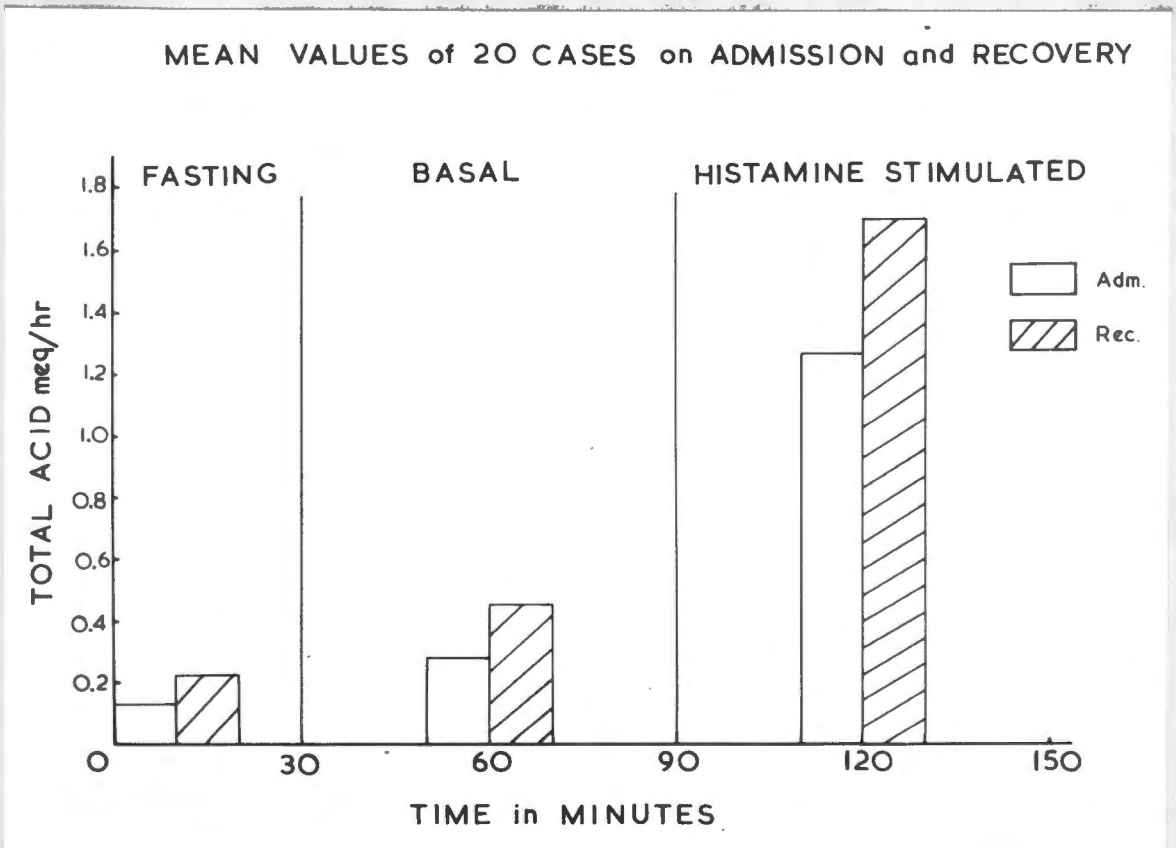
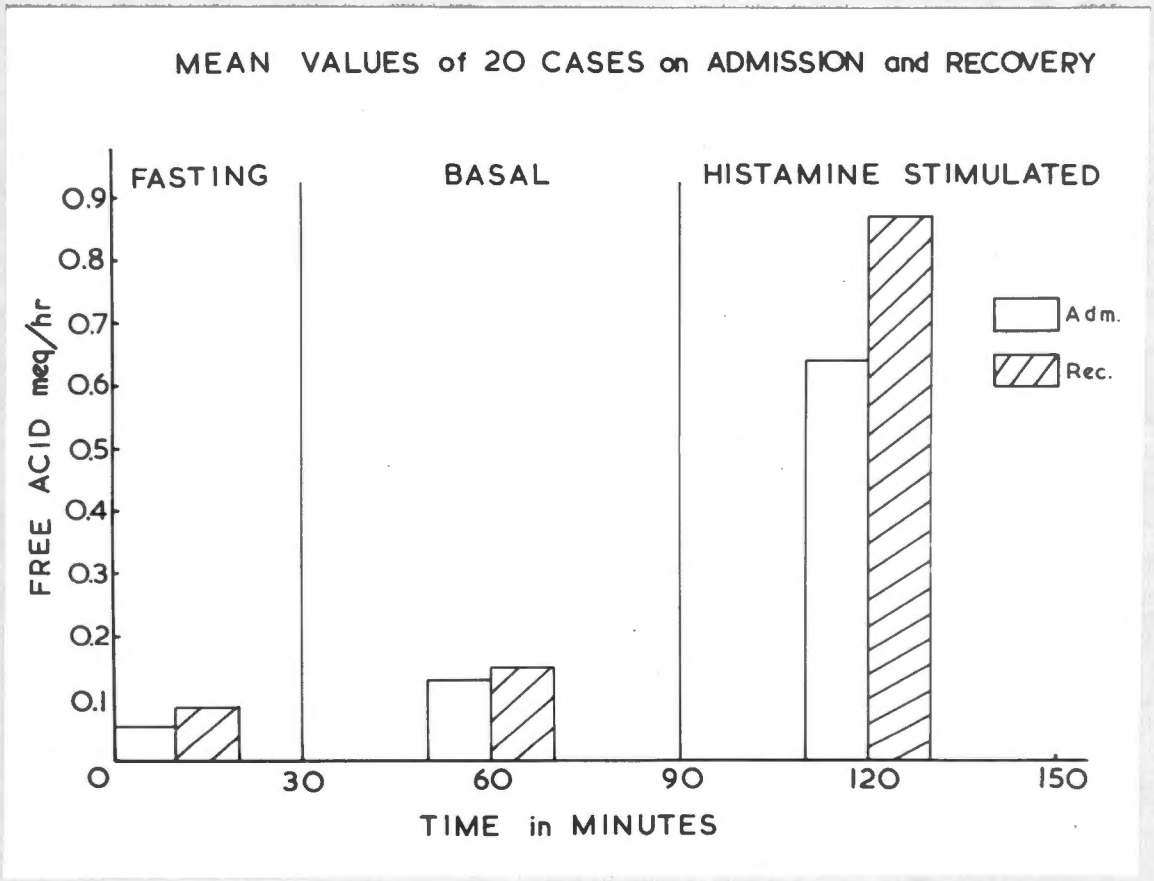


FIGURE. 49.

20 PATIENTS FREE ACID OUTPUT.



In Table 37a and 37b the clinical and test details of the patients are indicated. The age of the patient is indicated opposite the first test and the interval between the two tests is shown opposite the second test in the column marked "age".

The mean values on admission and recovery are given in Fig. 45-49 for all cases. Mean figures are used in the graphic illustrations for each of 3 periods i.e. fasting, basal and histamine stimulated indicating:-

1. The volume of fluid aspirated.
2. The lowest pH recorded.
3. The highest acid concentration recorded.
4. The total acid output.
5. The "free" acid output.

Fasting and basal acid output was often low and free acid was frequently absent. The pH tended to rise from the fasting to the basal samples in the majority of patients.

Maximum acid output was recorded about 15 minutes after histamine injection and persisted for about 30 minutes. By the end of one hour acid output was appreciably less again.

In the majority of patients on admission the pH dropped below 3.5 units on histamine stimulation and dropped by more than 1 pH unit. In 4 patients there was no drop in pH on stimulation and in 1 patient the lowest pH recorded was 4.39 units. This patient (G.D.) subsequently became totally achlorhydric and after a yean when re-tested, had improved considerably.

One patient (B.M.) had a good acid response on admission and deteriorated on recovery to a pH of 4.65. He was not tested again after this.

The values of the 16 patients who did show a response to histamine on admission are shown in Figs.50-54. It is seen that a larger volume of fluid

FIGURE. 50.

16 PATIENTS VOLUME OF FLUID.

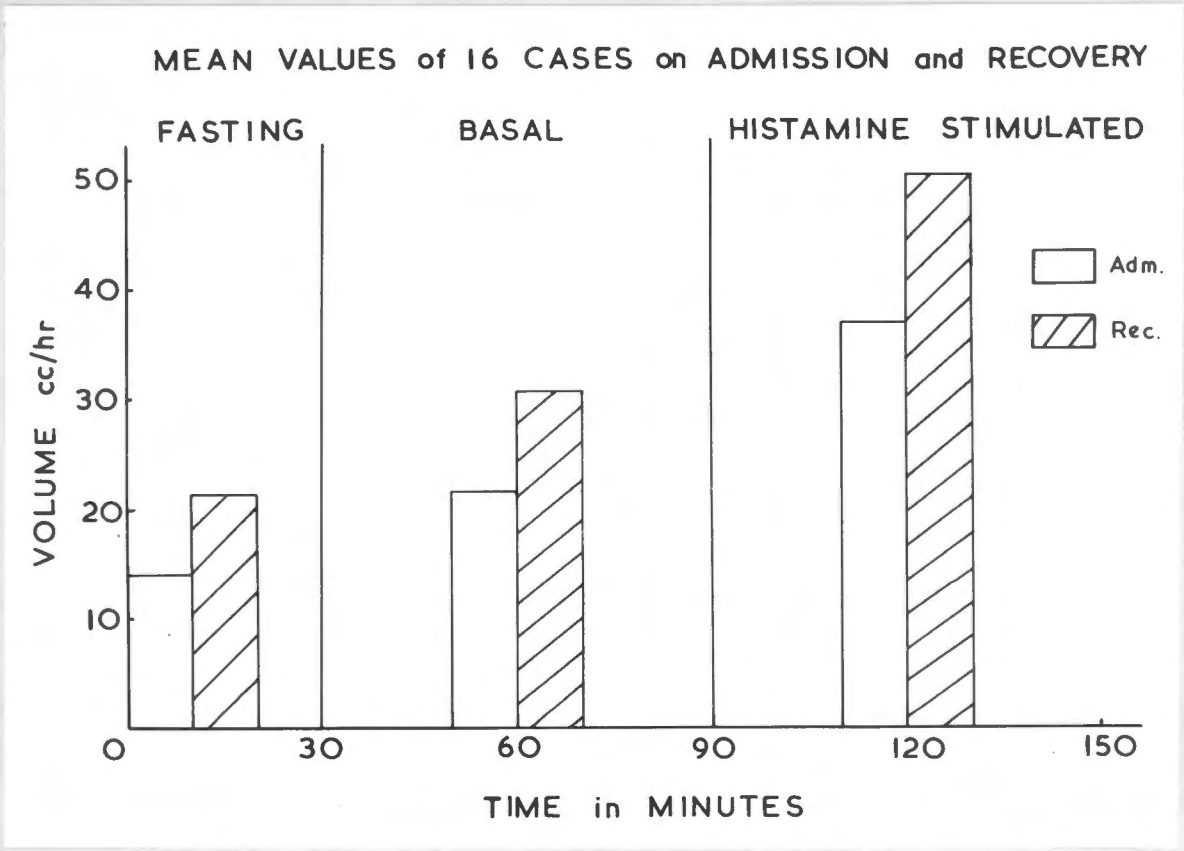



FIGURE. 51.

16 PATIENTS LOWEST pH.

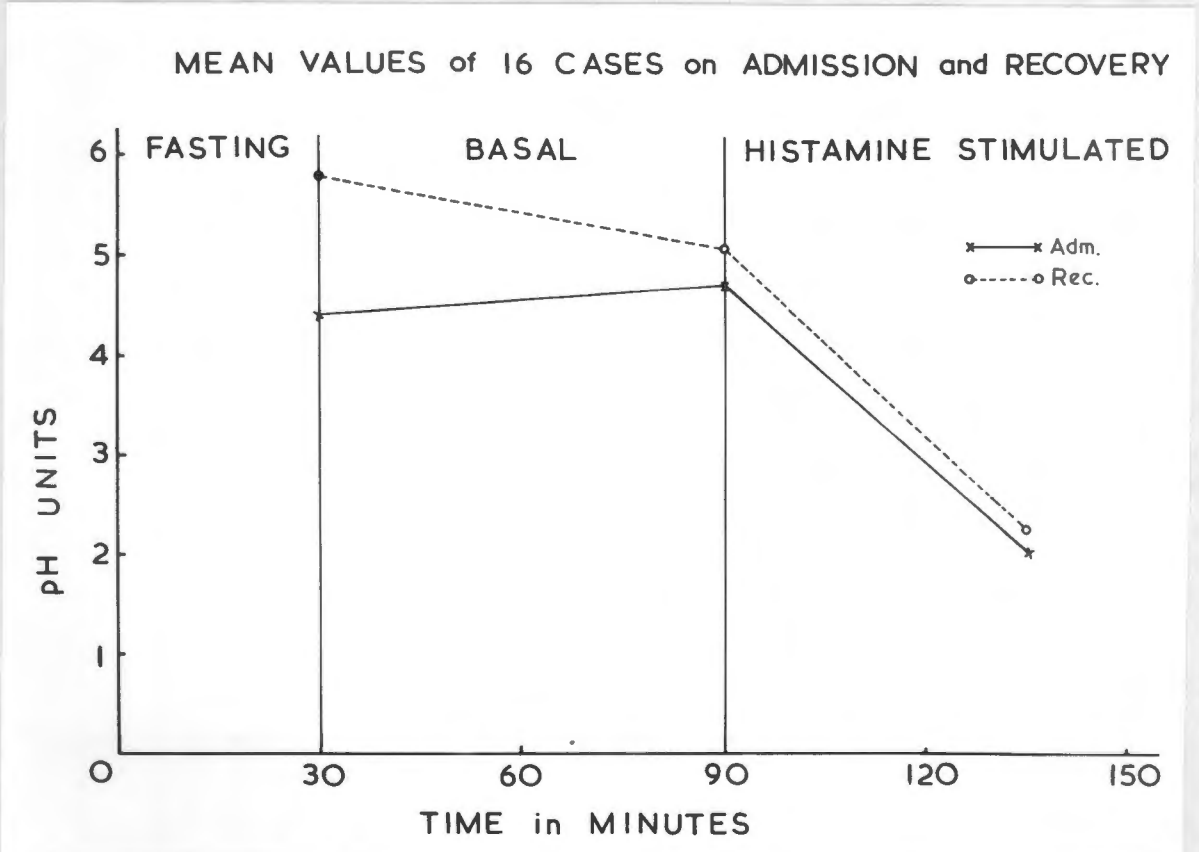


FIGURE. 52.

16 PATIENTS HIGHEST ACID CONCENTRATION.

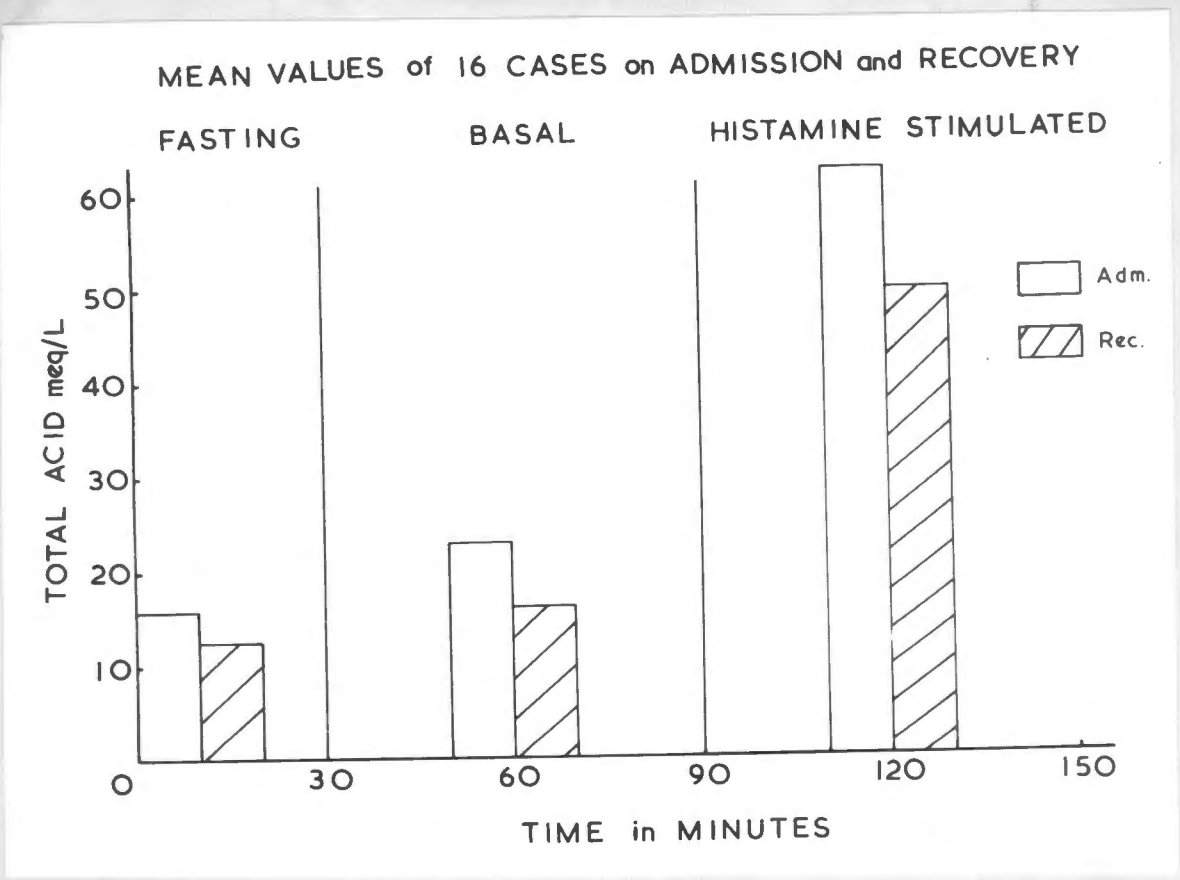



FIGURE. 53.

16 PATIENTS TOTAL ACID OUTPUT.

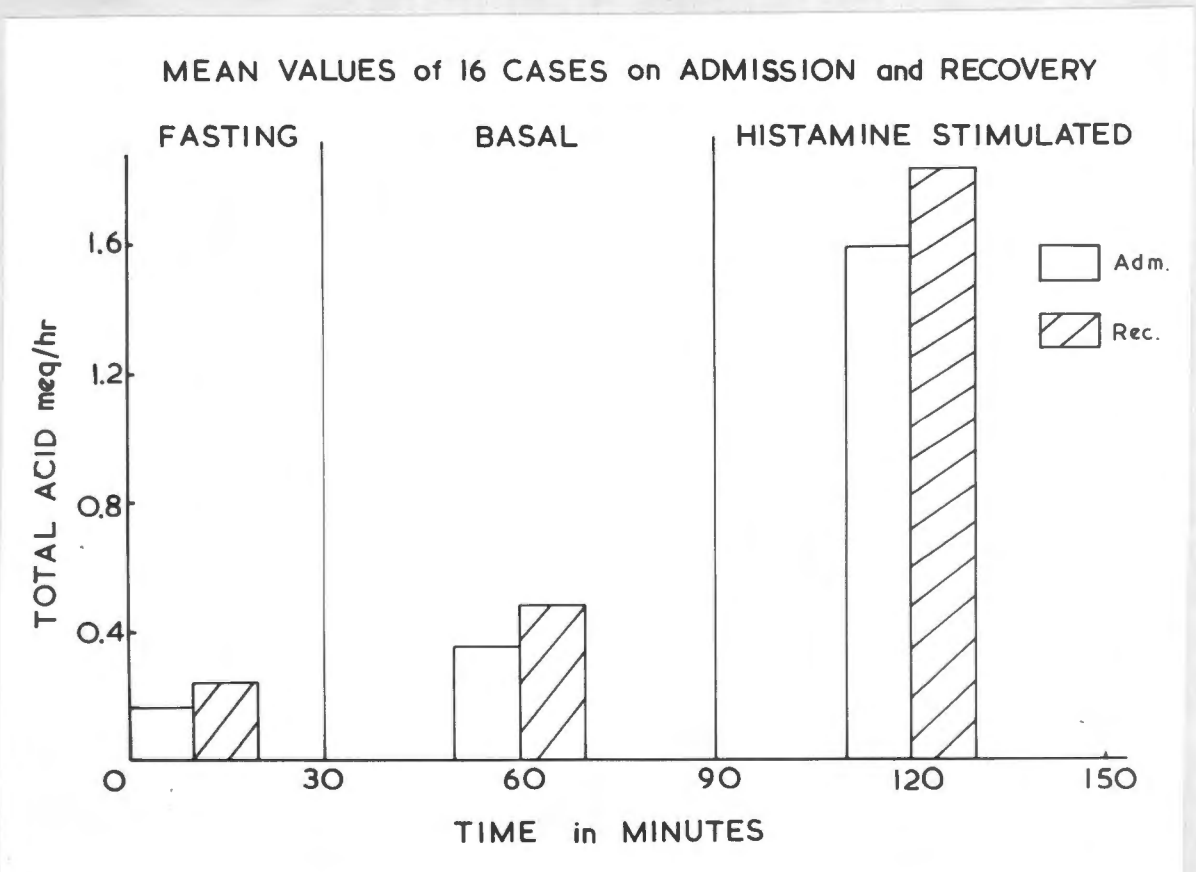


FIGURE. 54.

16 PATIENTS FREE ACID OUTPUT.

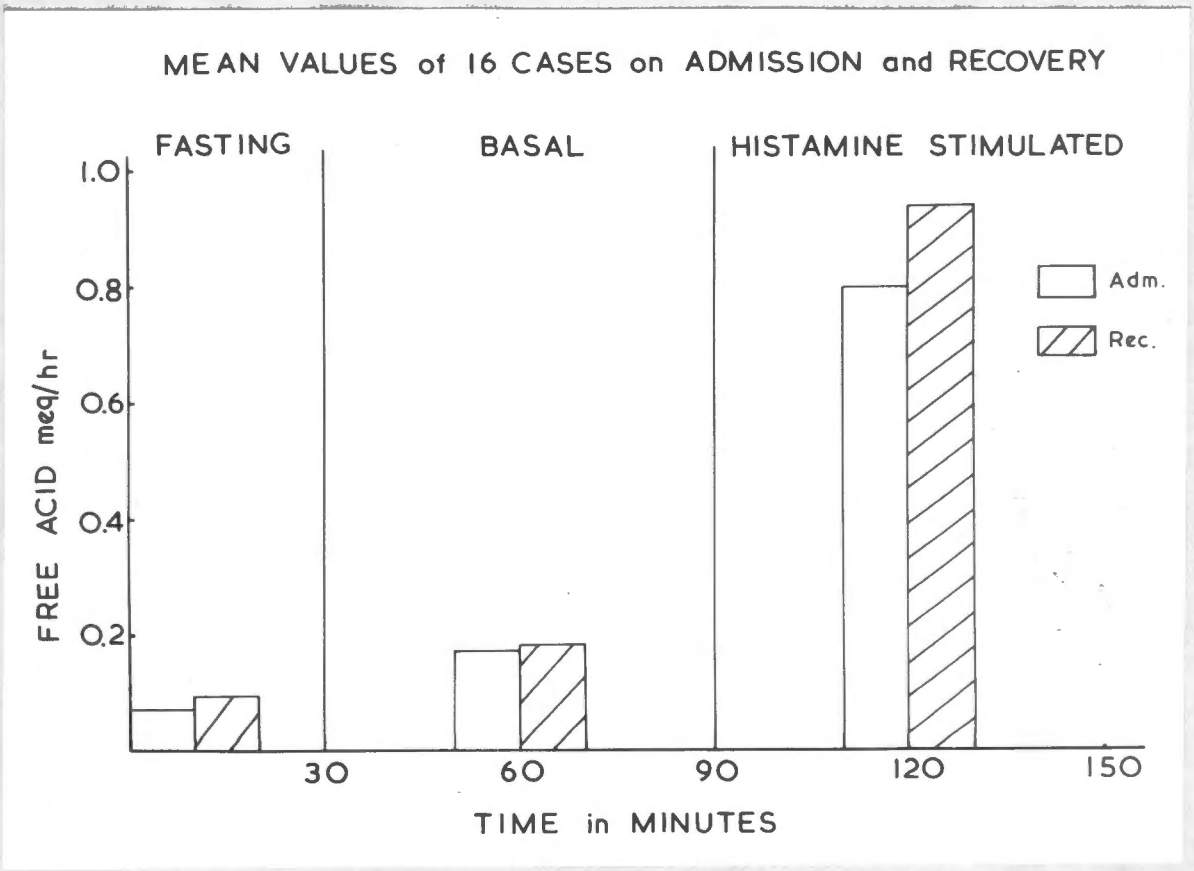


FIGURE. 55.

4 PATIENTS VOLUME OF FLUID.

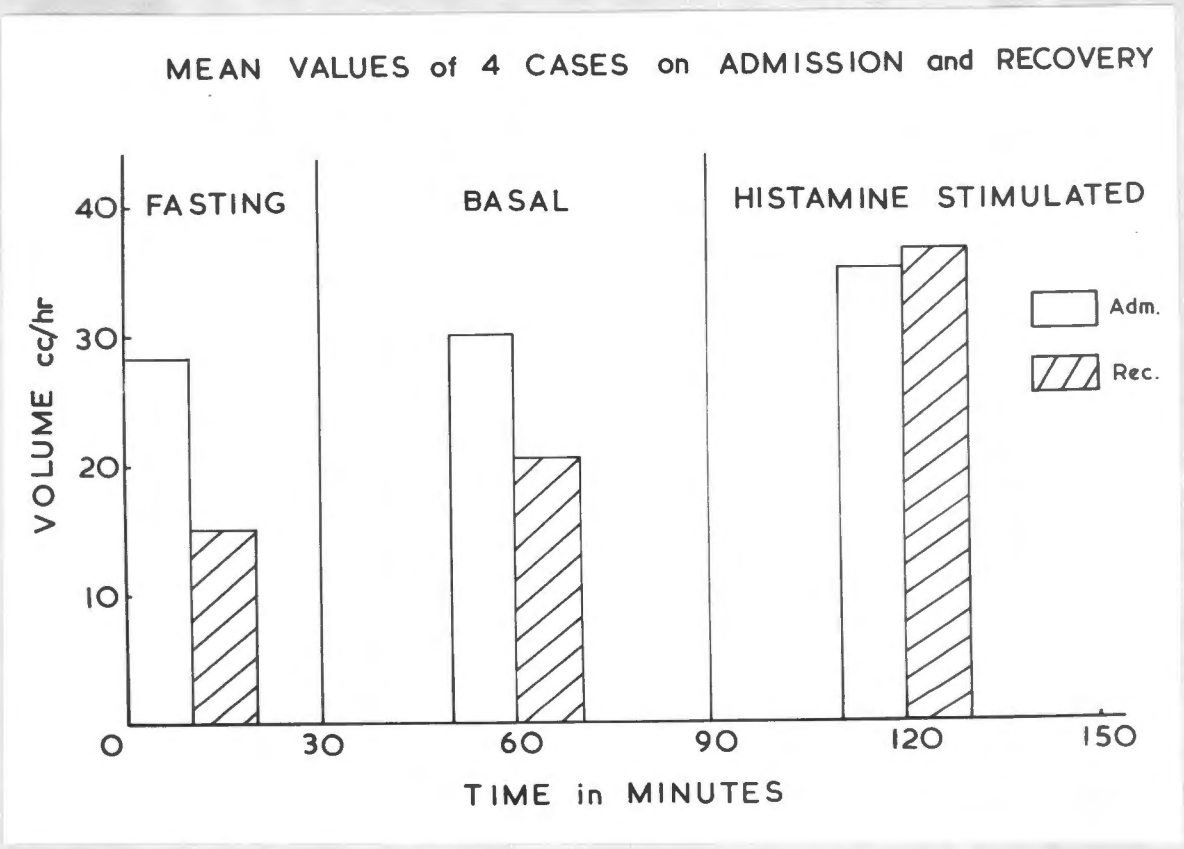



FIGURE. 56.

4 PATIENTS LOWEST pH.

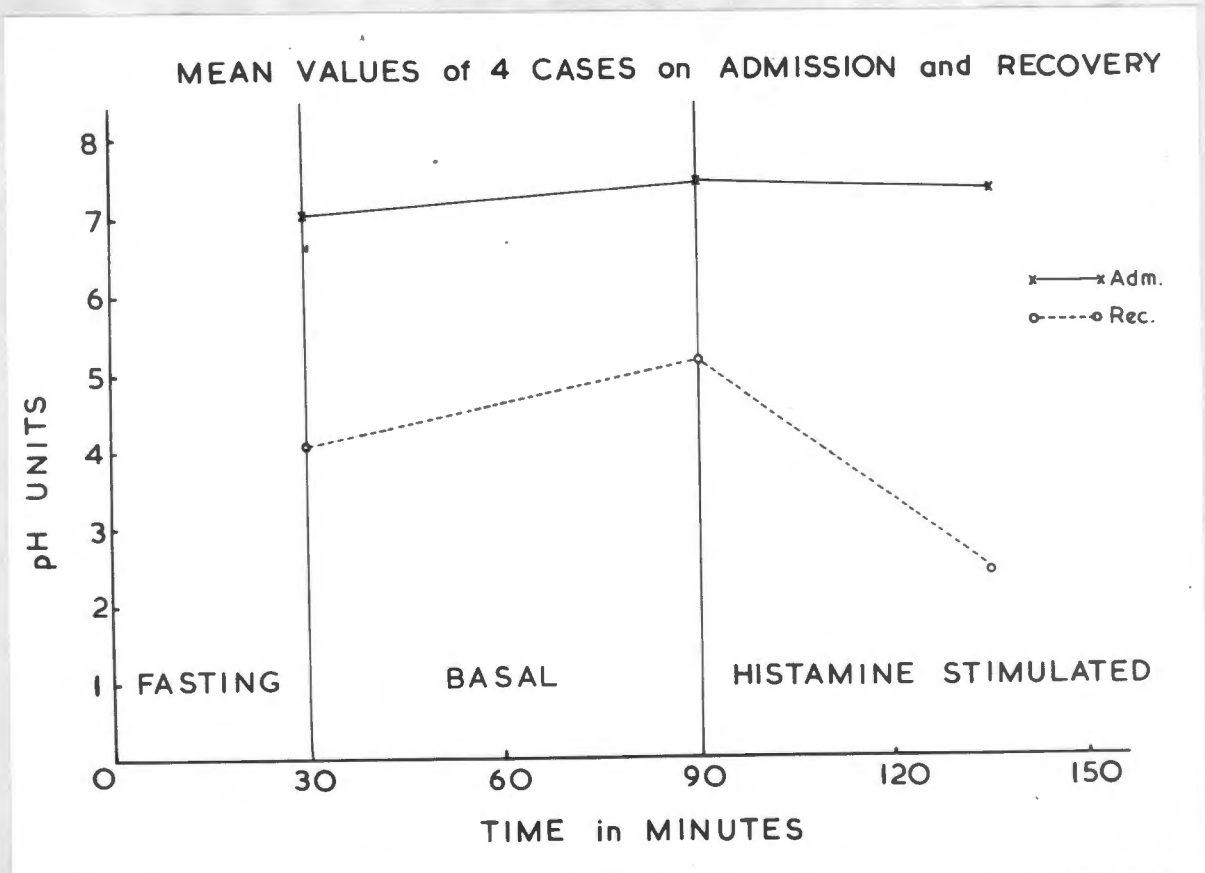


FIGURE. 57.

4 PATIENTS HIGHEST ACID CONCENTRATION.

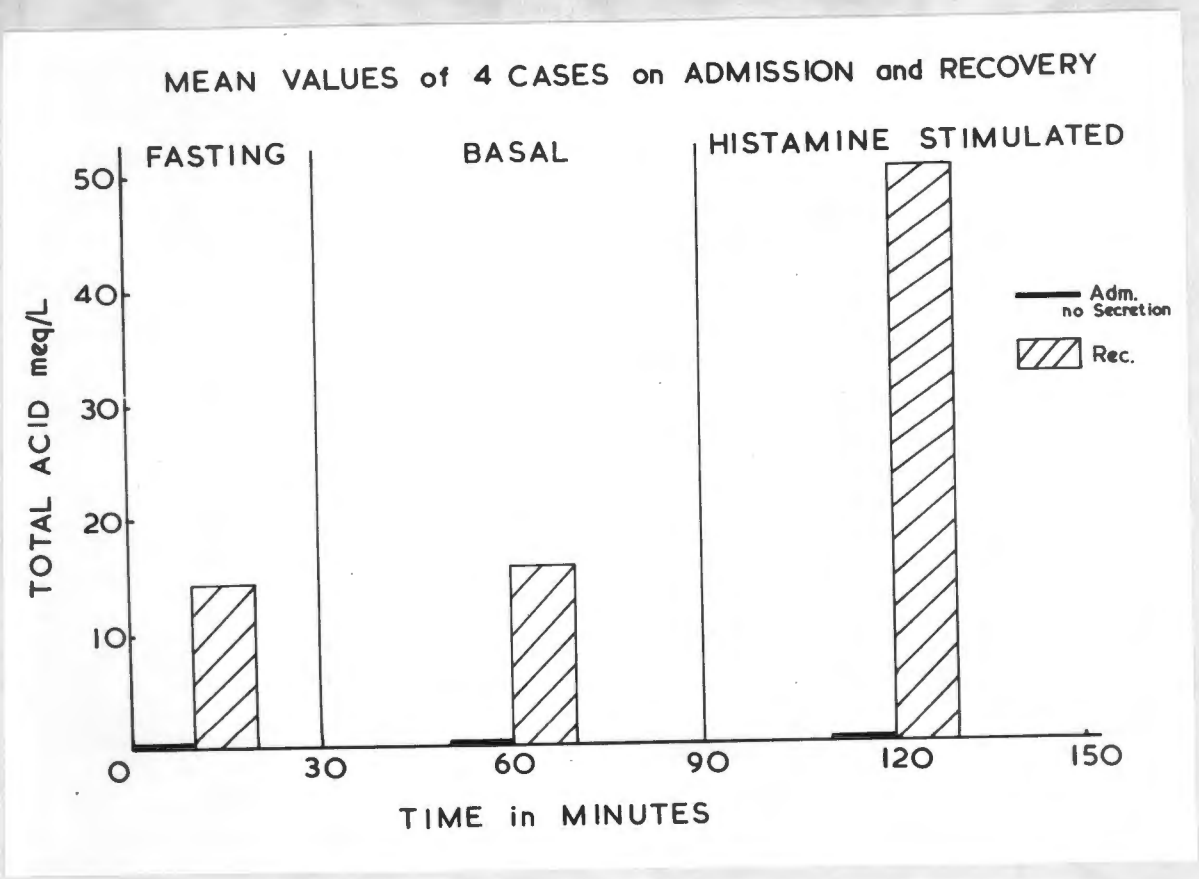



FIGURE 58.

4 PATIENTS TOTAL ACID OUTPUT.

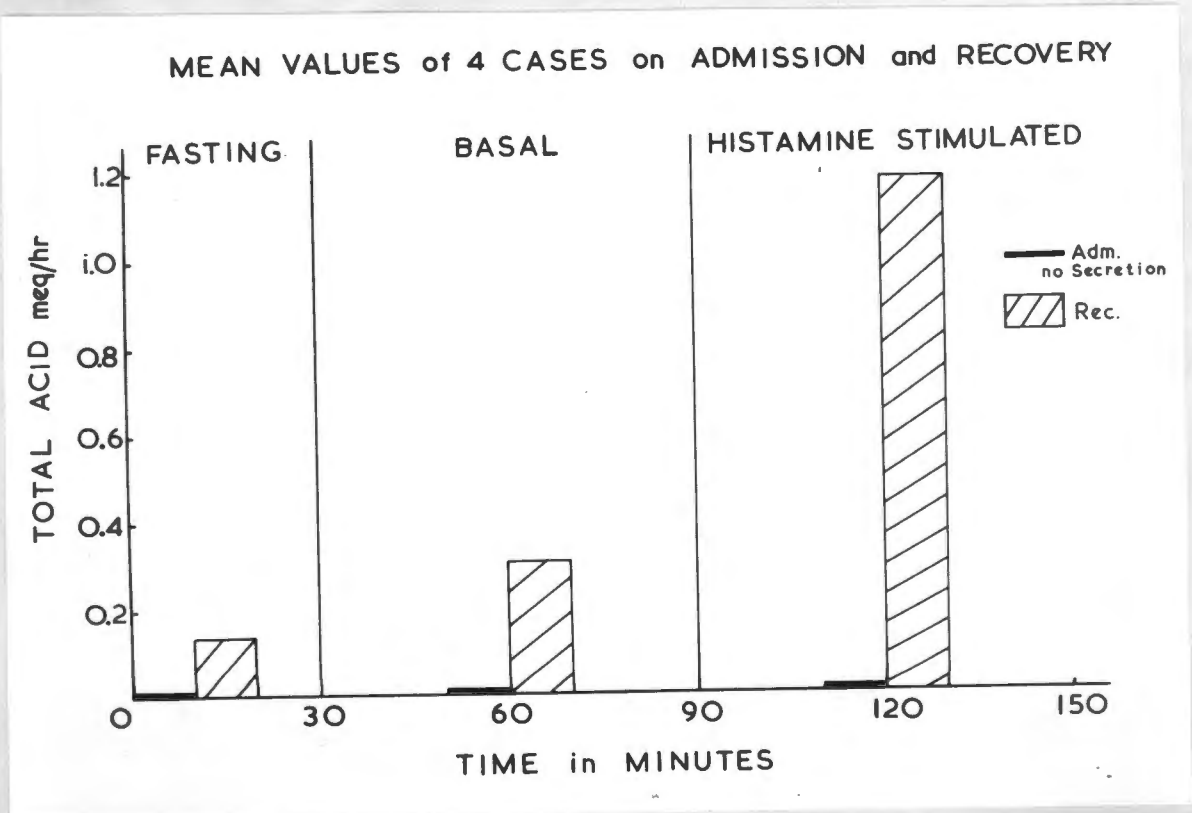
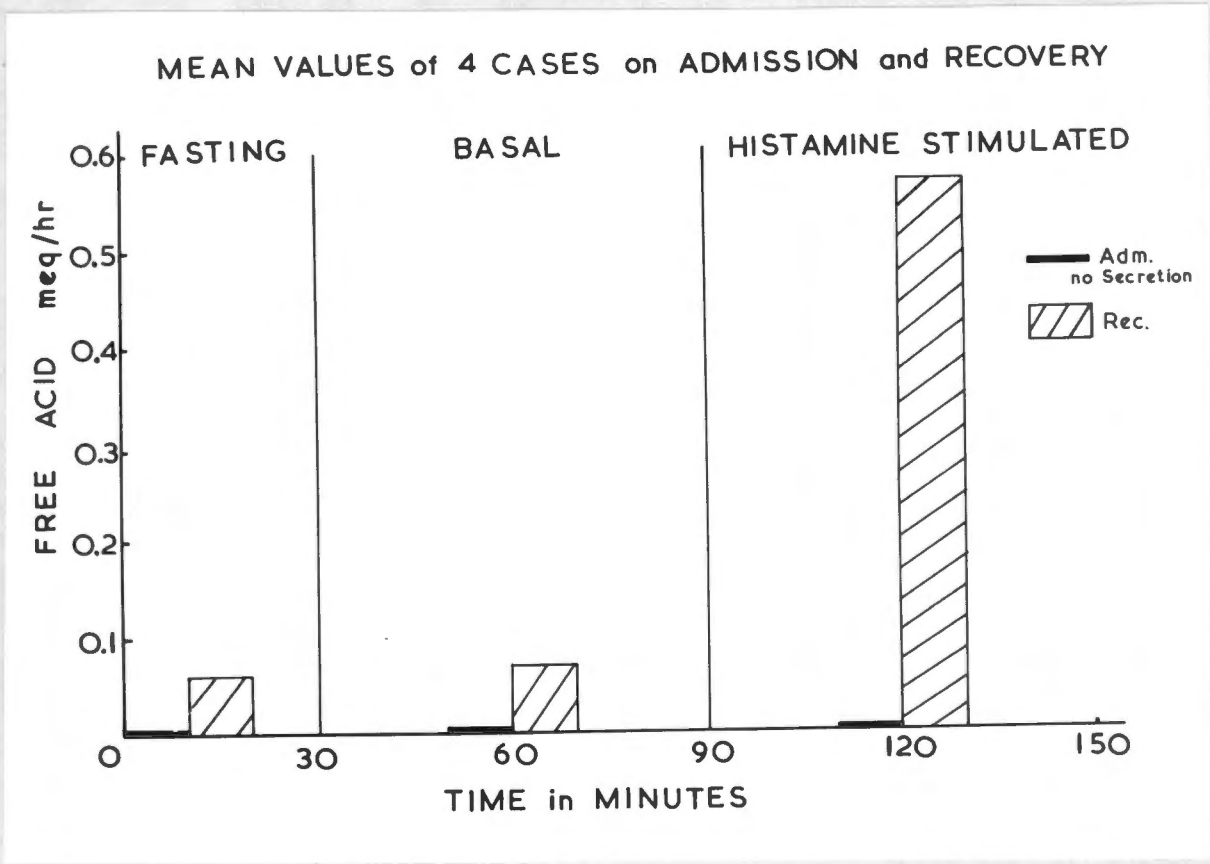


FIGURE. 59.

4 PATIENTS FREE ACID OUTPUT.



was obtained on recovery than on admission, while acid concentration was slightly but not significantly lower on recovery. The higher total acid output on recovery is therefore mainly due to the change in volume rather than in acid concentration.

The mean body weight of these patients was 8.5 kg. on admission and 9.2 kg. on recovery.

The 4 patients with achlorhydria on admission are demonstrated in Figs. 55-59.

On recovery the volume of fluid remained virtually unchanged while the acid concentration increased significantly. The total acid output was now comparable to the previous group. One patient (L.v.R.), although much improved, still had a low acid output. The pH dropped by more than 1 unit on stimulation but never dropped below 3.96 units. This patient was still anaemic at this stage, although he had been treated. The mean body weight of these patients had increased from 7.7 kg. to 9.1 kg.

Clinically there were no clear-cut differences between the patients who were achlorhydric and those who were not. The improvement in acid secretion followed the treatment of the anaemia rather than the recovery from kwashiorkor. The patient previously cited (G.D.) also improved only after treatment of the anaemia.

The gastric juice was not always examined microscopically. In those where it was examined pus cells, epithelial cells and bacteria were often present. This did not correlate with acid secretion.

Gastric biopsy was done in 5 patients, and one of these had 2 biopsies at an interval of one year. The details of these patients are summarised in Table 38.

One patient with achlorhydria had a normal gastric mucosa.

## GASTRIC BIOPSY.

| NAME | AGE | CLINICAL | | | | HISTAMINE TEST | BIOPSY RESULT |
|---|---|---|---|---|---|---|---|
| | | SKIN LESIONS | OEDEMA | SEVERITY | HB. G% | | |
| E.A. | 1.8/12 | Minimal | Moderate | Moderate | 8.45 | Lowest pH 4.40<br>No titration done.<br>Test not repeated. | Goblet cells replaced by simple columnar epithelium Lamina propria shows heavy inflammatory cell infiltration. Polymorphs and eosinophils predominantly. |
| A.J. | 1.3/12 | Minimal | Gross | Moderate | 7.7 | Lowest pH 5.53<br>No titration done.<br>Test not repeated. | Glands well formed with no evidence of atrophy. Trivial cell infiltration in superficial mucosa. |
| O.A. | 1.1/12 | Minimal | Slight | Mild | 9.7 | Total acid output on histamine stimulation 1.22 m.eq/Hr.<br>Test not repeated. | Slight oedema of lamina propria with mild diffuse increase in cellularity. Lymphocytes and eosinophils prominent. |
| O.D. 1. | 2.11/12 | Moderate | Moderate | Moderate | 8.9 | Total acid output 0.20 m.eq/Hr. pH 4.39 | Goblet cells replaced by inactive low cuboidal cells. Lamina propria crammed with plasma cells. |
| 2. | 3.11/12 | Nil | Nil | Nil | - | Repeat test after 1 year - Total acid output 0.34 m.eq/Hr. pH 1.59 | Repeat biopsy showed no change.<br>Child now clinically well. |
| L.v.R. | 1.11/12 | Nil | Moderate | Mild | 6 | Lowest pH 7.12<br>No titration done. | No histological abnormality detected. |

TABLE 38.

DETAILS OF GASTRIC BIOPSY.

The other patients with impaired acid secretion showed varying degrees of superficial mucous membrane atrophy and inflammatory cell infiltration.

The patient who was examined twice had improved but not fully recovered his acid secretion in the year. The gastric biopsy remained abnormal.

The one patient with a good acid response had a mild cell infiltration of the mucosa but no atrophic changes.

Although the tests were not adequately controlled and findings were variable, there appears to be some association between mucous membrane changes and impaired acid secretion.

The results of the study can be summarised as follows:-

Gastric acid secretion showed a good response to histamine stimulation in the majority of patients investigated. Where acid secretion was impaired it seemed to be related to anaemia rather than to severe protein deficiency per se. Total achlorhydria was present in 20% of cases and acid secretion improved in all cases who were tested after treatment of the anaemia.

Mucous membrane changes were not adequately investigated but the mucosa was more frequently abnormal than normal when acid secretion was impaired.

## THE INFLUENCE OF DEHYDRATION ON SERUM ALBUMIN CONCENTRATION AND BODY WEIGHT.

In the gastro-enteritis study the serum albumin dropped significantly on rehydration . Serum albumin in the third sample was significantly higher than immediately after rehydration (see Table 7.). The children were weighed at the time blood was taken. In Table 39 the changes in weight are shown.

Table 39.

| | Body weight in lbs. |
|---|---|
| 1. Dehydrated (Zero time) | 12.4 ± 3.62 |
| 2. Immediately after drip (24hrs) | 13.9 ± 3.64 |
| 3. One day later (48hrs) | 13.7 ± 3.95 |

Weight showed a mean increase of 11% after rehydration and did not change from immediately after rehydration to the following day. It is therefore unlikely that dehydration was responsible for serum albumin of the 3rd sample being higher than the second.

During the diet trial on gastro-enteritis patients the serum albumin changes were again studied in 14 patients. These needed no further I.V. therapy after the first 24 hours and remained clinically well hydrated. Body weight showed similar changes to the above.

The serum albumin changes of the diet trial are indicated in Table 40.

Table 40.

| | Serum albumin g% | |
|---|---|---|
| | Mean | Range. |
| 1. Dehydrated | 4.29 ± .84 | 3.14 - 4.93 |
| 2. Immediately after drip (24hrs) | 3.24 ± .54 | 2.42 - 4.56 |
| 3. One day later (48hrs) | 3.27 ± .44 | 2.67 - 4.44 |
| 4. Two days later (72hrs) | 3.34 ± .45 | 2.52 - 4.28 |
| 5. Three days later (96hrs) | 3.39 ± .44 | 2.65 - 4.12 |

The second sample was significantly lower than the first ($t = 3.933$ $p = < 0.001$). After this however, no significant change occurred in the albumin concentration.

The marked effect on serum albumin concentration due to dehydration is confirmed. Blood taken immediately after rehydration may give a falsely low result. Samples taken more than 24 hours after rehydration show insignificant fluctuations if the state of hydration remains good and no further intravenous fluid is administered.

## CHAPTER 4.

1. Discussion of results.
   - (1) Assessment of the nutritional status.
   - (2) Malnutrition and infection.
   - (3) Treatment of gastro-enteritis.
   - (4) Additional - a. Gastric acid secretion.
     - b. Nitrogen balance.
     - c. Influence of dehydration on albumin and weight.

2. Suggestions for the control of gastro-enteritis.

3. Summary and conclusions.

## DISCUSSION.

**Assessment of the nutritional status of the patients:**

Kwashiorkor and nutritional marasmus represent the extreme grades of protein-calorie malnutrition. They have become well known and easily recognised clinical entities.[84,132] The term protein-calorie malnutrition as suggested by Jelliffe includes all grades of deficiency of these nutrients.[133] Kwashiorkor and marasmus represent only a fraction of the total group which has been likened to an undersea mountain with only the tip protruding above the surface of the water.[134] The mild - moderate and easily reversible forms of the disease are as yet not generally appreciated or recognised by most medical men. Adequate treatment is consequently frequently delayed until the children present with a severe degree of the illness with a high morbidity and mortality. Clinical and biochemical signs usually appear late.[114,135].

Growth retardation is a constant early sign of the deficiency[114,136] and weight for age is a readily available measure of nutrition.[137] A grading of malnutrition by weight as proposed by Gomez[36] has been internationally accepted.[137] Ideally a growth record over a period of time should be compared to locally applicable standards[114] but such standards are not always available and, where malnutrition is prevalent, local growth charts are not likely to reflect the optimum growth potential of the population affected. That normal standards of other population groups could be applied more generally has been suggested by a number of studies. Under improved nutritional and environmental conditions the growth of the classically small Japanese can become comparable with American standards.[138] A socio-economic gradient of weights and heights has been demonstrated within ethnic groups where weights and heights of the more favoured sections are comparable with European standards while the others are much lower.[139,140]. In poor or underdeveloped communities growth during early

months of infancy is often comparable with Western European standards but starts deviating below them when diet becomes less adequate after weaning.[84,128.]

From the data presented in this study it is suggested that the American growth charts are applicable to the population studied and that the vast majority of children whose growth diverges from them are suffering from nutritional growth failure. The major part of the problem of malnutrition is not reflected by the incidence of kwashiorkor but by the incidence of severe gastro-enteritis in malnourished children. Unless this association is appreciated treatment and prevention programmes will remain inadequate.

Emphasis in this investigation was mainly on the protein nutritional status of the children studied. The associated deficiencies that were found, such as anaemia and rickets, serve to stress the general tendency for deficiency states to be multiple.[85,86.]

Weight and serum albumin: Hypo-albuminaemia is an accepted measure of protein malnutrition.[32,122,137.] It is, however, not a sensitive index and a low serum albumin probably reflects an advanced degree of depletion of the total albumin mass.[141,142.] The fact that laboratory facilities are necessary for its estimation further limits its general use in common with other biochemical indices of malnutrition.

Weight for age is generally available and, in addition, low weight occurs early and constantly in the presence of malnutrition.[114,137.] The importance of low weight as an index of malnutrition was confirmed by this study.

Whenever the body weight of the patients was normal by American standards, the serum albumin was normal almost without exception. The incidence and degree of hypo-albuminaemia increased progressively with increasing weight loss. This was found in symptom-free children as well as in patients with gastro-enteritis. In gastro-enteritis the serum albumin may be influenced by

anorexia with additional starvation and malabsorption. This may explain the fact that normal weight gastro-enteritis patients had a lower mean serum albumin than the controls although they were still within the normal range. The duration of the illness, however, did not significantly influence the albumin but the correlation between hypo-albuminaemia and low weight was striking.

Additional evidence of nutritional growth failure was found in the close association between low weight and low protein intake. Low weight and inadequate milk intake occurred with progressive frequency with advancing age. Previous workers have found the weight of the same population comparable to European standards during the early months of infancy and demonstrated a divergence after feeding became less adequate.[84,128] Jelliffe[16] indicated that malnutrition heads the list as a cause for this divergence.

Height, Weight and Bone Age: Growth failure is reflected by both low weight and a low height for age. It is often stated that the height is much less affected than the weight.[114,143]. In addition, retarded bone age has been demonstrated in malnourished children.[136,144,145] In robust and wellnourished children even a severe illness would only have a temporary effect which is rapidly obliterated on recovery.[136,146].

The children investigated here often showed gross stunting and severe retardation of skeletal maturation. Superficially they appeared well proportioned and were frequently well covered with subcutaneous fat. This deceptive appearance of grossly retarded children has often been recorded in the past.[16,96,147]. It is an important practical point, because malnutrition would not be diagnosed in such a child unless his weight were compared to the normal for his age. A close association was demonstrated between weight and height in relation to the normal percentiles. The children who were normal in weight were usually also normal in height. In particular the children above the 10th percentile in weight tended

to be normal in height although the weight was usually in a higher percentile than the height. Stunting was more marked in those children who were more grossly underweight.

It is not surprising that weight and height are not always absolutely comparable. Fluctuation in weight can occur rapidly while the height remains static or increases slowly so that low weight can become more rapidly apparent than a low height for age. With recovery, children commonly gain weight more rapidly than height.[95] This phenomenon was well illustrated in this study by the number of post-kwashiorkor children who gained weight into the normal percentile range but lagged behind in height. It is known that some of the other children had gained weight into the normal range but their original heights were not known.

The genetic influence on growth in this population has not been established and it must be considered that some children may be genetically short. It has been suggested that malnutrition over several generations may influence the stature of the population. A degree of "genetic segregation" may occur in that individuals of relatively slow growth and small adult size are more likely to survive in an impoverished environment.[139] In the unit in Cape Town an investigation is at present being done to study growth with optimum feeding from birth, in families where previous children are known to be underweight and stunted. No results are yet available.

The studies on height/weight ratios were interesting. It was clearly demonstrated that both the normal weight and the low weight children were essentially well proportioned and comparable to American standards. This would obviously not necessarily be true in acutely ill patients who had recently lost weight rapidly. For this reason such children were excluded from the study.

A disturbance of this ratio has been demonstrated in kwashiorkor and marasmus and it has a certain prognostic value.[148] Only when a normal ratio has been restored, even if both weight and height were still abnormal, does the prognosis become good. This demonstrates the importance of distinguishing between ill children and well children when comparing height/weight ratios.

Expressing both the weight and the height as a percentage of the expected mean does not convey the same degree of abnormality. At a given age a 3rd percentile weight is 80% of the mean and a 3rd percentile height is 93% of the mean. Normally the birth weight is doubled in the first 6 months of life. The length at birth is only doubled by the age of 4 years.

For this reason it is suggested that height and weight be treated in different ways when compared with a normal range of percentiles.

In a group of children including some normal and some abnormal weights and heights it became apparent that the mean percent expected weight was 85% and the mean percent expected height was 89%. If the normal and abnormal are separately analysed it transpires that the normal weight children have a mean weight of 96% and the abnormal 68%. The heights of these children were 94% and 83% respectively. It has been shown that both the normal and the low weight children have a normal height/weight ratio and yet from the above figures the low weight children have apparently lost weight to a much greater extent than they failed to grow in height. However when compared in inches grown from birth the retardation is much more evident. Thus the low weight children had grown only 15" instead of 22" since birth. The normal weight children had grown 15" instead of 17"

Expressing the actual growth in length as a percentage of expected growth in absolute terms gives a figure which is much more comparable to the percent expected weight. It also gives a figure which indicates that low weight

is proportionate to the failure of growth in height. Further evidence of a normal height/weight ratio is demonstrated by the figures on the kwashiorkor follow-up series. The children are almost perfectly in proportion for weight and height at a given bone age to a normal child at the same chronological age.

Further studies on bone age are indicated. The results were difficult to interpret because of the unequal retardation of some centres compared to others. This phenomenon has been previously described.[136,145] Furthermore, there is evidence to suggest that European standards in this respect may not be applicable to non-White racial groups because bone maturation may be normally advanced in the latter.[136,149] The retardation demonstrated in this present series is even more striking if these observations are correct.

By the above standards severe malnutrition was common among the kwashiorkor siblings and in the gastro-enteritis patients. Only a very small proportion of these children developed kwashiorkor. A diagnosis of protein-calorie malnutrition was justified in the majority of the Cape Town children if the weight fell below the normal range of American standards. Additional evidence of malnutrition was present in the majority of underweight children. Low weight can be used for diagnosis if facilities for other investigations are not available.

The gross degree of growth retardation in this study was very striking. The deceptive appearance of retarded children and the lack of clinical signs even when gross hypo-albuminaemia is present have been stressed. The late appearance of biochemical signs has been indicated. Changes of body composition which would be normal for healthy but younger children have been demonstrated in many of these children.[150] Gomez et al[113a-c] suggested that such children adapt themselves to their metabolic status by slowing or almost complete cessation of growth.

They pointed out that malnourished children are not only structurally but also biochemically different from wellnourished children.

The abnormalities of composition and of growth both suggest that many malnourished children have the characteristics of much younger children. The practical implications of these findings regarding management and therapy during any illness of such children are important.[151]

Early diagnosis of malnutrition would prevent the high morbidity and mortality from gastro-enteritis and more extreme degrees of malnutrition. Low weight for age is stressed as a valuable early sign.

## MALNUTRITION AND INFECTION IN GASTRO-ENTERITIS.

A strikingly high incidence of severe malnutrition has been clearly demonstrated by the findings in this study.

Important differences in diarrhoae morbidity and mortality became apparent by comparing the normal weight children with those who were below normal in weight. Severe recurrent diarrhoea was strikingly more common in the low weight children and mortality was more than double that of the normal weight children. Poor socio-economic circumstances were closely associated with malnutrition and the progress of the child could, with a high degree of accuracy, be related to this factor. Milk intake and therefore protein intake was totally inadequate in the majority of low weight children. A prolonged episode of diarrhoea alone did not make a significant difference in the serum albumin. After treatment, recurrent diarrhoea continued to be more frequent and more severe in the low weight children. These factors are strongly suggestive evidence that diarrhoea is severe and recurrent in a malnourished child and that the child is not primarily malnourished because he has recurrent diarrhoea. Each episode of diarrhoea would further increase the malnutrition especially as these episodes so frequently are followed by prolonged periods of starvation. The majority of normal weight children remained normal in weight at follow-up. These were the children with a more satisfactory and adequate home environment.

In the younger age groups the disease was present in both malnourishe and wellnourished children but after the age of 15 months it occurred almost exclusively in the severely malnourished children.

Infection: Infection occurred with almost equal frequency at all ages and it was not more frequent in the malnourished patients. Although specific entero-

pathogens were not isolated with any great frequency, suggestive evidence of infection was present in the majority of cases. Shigella may have failed to be isolated in some of the patients who had pus, mucus, red cells and macrophages in the stools. A reduction in the positive culture rate may have been influenced by treatment prior to admission. An adequate assessment of this factor could not be made because the patients rarely knew what type of medicine had been prescribed. A higher incidence of infection may have become evident if (a) Virus studies had been done and (b) E.coli had been looked for in both trials instead of only one.

However in a recent study in Johannesburg Kahn et al[68] were unable to demonstrate a significant relation between diarrhoea and enteroviruses. When present, the disease is believed to be mild and of short duration.[8]

The incidence of E.coli in patients and controls in this study was not significantly different. A similar observation was made in an earlier study on diarrhoea in Johannesburg.[62] E.coli diarrhoea had most commonly been found in newborn babies and infants under 1 year in institutions.[8,59] The disease is mild and often infected babies have no symptoms. Little is known of the importance of E.coli in the diarrhoea of malnourished children.[77] From the small number of cases in this study conclusions cannot be more than tentative. In general the findings fit with previous reports. The infection occurred under 1 year old and the prognosis was good. In the diet trial done subsequently the organism was not isolated in any of the patients investigated, indicating that the infection does not only vary from place to place but also from time to time.

A striking difference in the incidence of worms and giardia and multiple infections was found between the older malnourished patients and the younger less malnourished children. Here it was not possible to determine the relative importance of age and malnutrition. Age almost certainly is a factor

but in the light of previous work it is more likely that malnutrition was the deciding factor. Malnourished animals have been shown to have an increased susceptibility to helminthic infection[152] and multiple intestinal parasites in man are more commonly found in malnourished poorer classes.[153] Although the morbidity due to worms cannot be adequately assessed[73] the additional nutritional hazard of infestation in malnourished children has been pointed out by Jelliffe.[16] An amazing number of adverse factors capable of aggrevating malnutrition are concentrated upon these older patients with gastro-enteritis.

Infection was so frequently present that it must be considered the most common precipitating cause of diarrhoea. It was, however, equally common in wellnourished and malnourished patients. In the wellnourished patients this did not seem to affect the subsequent progress of the child adversely. The malnourished child had recurrent and often severe episodes of diarrhoea. This aspect needs to be emphasised. The important practical consideration is not whether infection or malnutrition is the more important factor in the causation of diarrhoea. The outstanding fact is that this type of diarrhoea occurs in malnourished children far more frequently than in wellnourished children. Elimination of infection would obviously improve matters and perhaps reduce mortality. It would not restore normal growth in such children[134] and would not prevent similar subsequent episodes.

From this work it is not possible to define the relative importance of infection and malnutrition. Almost invariably the first attack of diarrhoea followed soon after the introduction of bottle feeds. Adequate food intake dropped progressively and one attack of diarrhoea followed another. Infection and malnutrition, as it were, both have their origin in the feeding bottle and cannot be separated after this. A home environment which favours frequent infection also favours the development of malnutrition in its own right.

Multiple factors were involved in the production of this type of severe recurrent diarrhoea. The outstanding feature was the nutritional status of the host and this appeared to determine the course of the disease more than any other single factor. Considering all the factors, including the degree of malnutrition and frequency of infection, mortality was surprisingly low.

Without intensive therapy, however, the mortality is high[38] and malnourished children often die of infections which would resolve spontaneously in wellnourished children.[45]

Much confusion exists on the importance of infection as a cause of malnutrition quite apart from the controversy about its role in the causation of diarrhoea. Several aspects of this association are illustrated in a recent article by Ryan et al.[154] They indicated that " it is generally accepted that marasmus is related to infection or underfeeding". From their investigation they concluded that malnutrition in the majority of cases was precipitated by infection. Gastro-enteritis is listed as one such infection without any evidence to show that the diarrhoea was infective in origin. "Malnutrition" which covers a wide range of deficiency diseases[133] was in this context confined to marasmus and kwashiorkor. In a very good discussion the authors then point out that malnourished children, as a result of infection, often develop a state of more profound malnutrition. This is the important concept. Malnutrition which already exists as the result of dietary deficiency is aggravated by infection. The infection may have a major influence on the prognosis of such severely malnourished children.[90,102].

It appears that severe gastro-enteritis is often the result of an abnormal response of a malnourished host to infection or other stresses. In the treatment and prevention of diarrhoea emphasis must be on the basic malnutrition rather than merely treating the infection when the patient presents with diarrhoea.

## THE TREATMENT OF GASTRO-ENTERITIS.

The project presented was not designed primarily to determine the best therapeutic régime in gastro-enteritis, but two aspects were covered:-

a. An Antibiotic Trial.

b. A Diet Trial.

### A The Antibiotic Trial.

Previous workers have indicated the striking effect of supportive therapy in the treatment of gastro-enteritis.[29,30,155,156] Varying success has been claimed with a variety of antibiotics. The British Medical Research Council[155] found results with Sulphadiazine better than with any other drug used, but reported Chloramphenicol also good. Stein et al[51,52] invariably found Chloramphenicol superior to other drugs. In these papers the results are not analysed in relation to the nutritional status of the patients and the term Chloramphenicol is used (correctly) but they do not indicate whether the fatty acid compounds for oral administration were used or not. Friedman[24] found results poor with a number of antibiotics in a group of children with severe malnutrition. Neomycin was found highly effective in the treatment of E.coli diarrhoea.[157] Since the introduction of antibiotics E.coli diarrhoea has apparently become much less severe.[8] Smythe[102] suggested that a combination of broad spectrum antibiotics given at frequent short intervals had advantages over other régimes in severely malnourished children.

In this work the important difference in response between the two régimes was apparent in the malnourished children who had enteral infection. Sulphadiazine and Penicillin gave better results than Chloromycetin palmitate. Such a difference had not been previously reported.

It is suggested that the failure of Chloromycetin was due mainly to

a combination of three factors:-

(a) The severe intestinal hurry.

(b) Impaired lipase activity.

(c) The long interval between doses.

The diarrhoea was more severe in patients with enteral infection than in those without. The drugs would therefore pass through the gastro-intestinal tract very rapidly. This might influence the activation of the Chloromycetin which probably needs a period of time in contact with the enzyme. In a well controlled in vitro experiment at the Red Cross Hospital, Norcott and McKenzie[158] were able to confirm the fact that Chloromycetin palmitate is biologically inactive.[159] They were able to show that the growth of Staphylococcus aureus is only inhibited after activation of Chloromycetin palmitate with pancreatic lipase. The deficiency of pancreatic enzymes in protein-calorie malnutrition[93] and following infections[97] has been adequately demonstrated.

These observation will have to be confirmed by further work under strict experimental control before any definite claims can be made.

From the work presented, Chloromycetin showed no advantages over Sulphadiazine and Penicillin in any of the groups compared. Although the latter two cannot, on the available evidence, be recommended as drugs of choice for routin use, they could under the circumstances be used in preference to Chloromycetin palmitate.

It has been indicated previously that control of infection may not automatically control diarrhoea.[3] The importance of supportive therapy in the management of diarrhoea has been repeatedly stressed.[29,30,155,156]. While certain infections may spontaneously resolve in wellnourished children they may be lethal to a malnourished child.[2,45] Smythe[102] stressed the tendency

towards gram negative bacterial septicaemia in severe malnutrition and advocated intensive antibiotic therapy in such patients and frequent oral administration if diarrhoea is present. The management is therefore again influenced by the nutritional state of the patients. Although no conclusive evidence is available regarding the most suitable drugs, it would be unwise, on present evidence, not to use antibiotics in the treatment of diarrhoea in malnourished children. Antibiotics alone are quite clearly not sufficient and treatment of the malnutrition must be a major consideration in management.[134]

Furthermore the high incidence of worms and giardia in older children with gastro-enteritis in Cape Town would justify routine therapy for these parasites. This has been successfully done in other parts.[153]

The Diet Trial in Gastro-enteritis.

Considering the variety of factors involved in the production of the disease this trial had not been well designed. Numbers are too small to draw definite conclusions.

In general the results are in agreement with recent findings by Bowie[101] in the same unit who found that response to the lactose-free diet depended on the presence of fermentation and was not influenced by the presence or absence of infection. In this trial the diagnosis was not established before treatment was started and much valuable information was thus lost. The patients who did not respond to the Casilan diet may not have had a fermentation diarrhoea. In the patients on milk, diarrhoea was severe in the presence of fermentation and response appeared to be dependent on its presence or absence. It must also be added that nitrogen intake was high and stool weights might have been lower with less intake. Children often appeared well and gained weight while still having frequent large stools.

It can be said that there is as yet no firm indication for the use of lactose-free milk routinely in the management of gastro-enteritis. However, in selected cases,it may make all the difference between failure and success. The first criterion for the use of lactose-free milk would be evidence of fermentation diarrhoea (judged by the lactic acid content of the stool) and not the nutritional status of the child.

Further work is necessary to confirm these observations. It would be an advantage to have an easy test for the diagnosis. Lactic acid estimation is an involved procedure and would not be an easy investigation to employ in a routine laboratory. The pH of the stools has been found unreliable as a diagnosti test.[101] In persistent cases a therapeutic trial might be used. The response is usually dramatic and a failure of response would negate the diagnosis.

## ADDITIONAL RESULTS.

1. The gastric acid secretion in kwashiorkor:

The augmented histamine test has not been widely used in young children although two recent reports indicated its use.[104,160]

A maximum dose response has not been established for children although Hirshowitz[160] found the acid output per kg. body weight the same in children as in adults with 4 body weight doses (0.04 mg/kg.) of histamine. His series was very small and some of the children were older than those in this study. No other reports were found on normal children. Although half the dosage used in this study would probably have been sufficient to produce maximum stimulation it can be said that this high dose was safe.

The test, although technically difficult in small unco-operative children, can with some experience be used successfully and with safety. Although bleeding was a constant worry, it was never excessive and no other major side effects were encountered. The occurrence of bleeding is probably related to some degree of superficial gastritis which was found on biopsy and has been previously reported in association with kwashiorkor.[102] and achlorhydria from other causes.[103,104]

Acid secretion was present in the majority of patients and the output on a body weight basis was in agreement with previously reported findings.[160,161]

Achlorhydria was apparently associated with anaemia rather than protein malnutrition per se. An improvement followed in all cases tested, upon treatment of the anaemia. This confirms the findings of other workers reporting on anaemia and achlorhydria.[104,105b,106].

From these data it is therefore unlikely that the protein deficiency found in gastro-enteritis led to achlorhydria and an increased susceptibility

to infection and diarrhoea as suggested by Kahn.[20] A relationship to anaemia in these patients seems more probable and therefore achlorhydria may well be an additional aggravating factor of diarrhoea in anaemic patients. The incidence of achlorhydria is not high and response to therapy is good. Anaemia occurs frequently in these patients[105] and, considering the gross disturbances related to this,[104] careful attention should be paid to the diagnosis and treatment of anaemia in patients with severe gastro-enteritis.

occurred in the albumin concentration if hydration remained satisfactory without further intravenous fluid administration.

It appears therefore that the sample taken when the patient is dehydrated gives a falsely high value. It is advisable to allow some interval for equilibration after rehydration. From available data this interval should be 24 hours or longer. An optimum time-interval has not been firmly establishe

## RECOMMENDATIONS FOR THE PREVENTION AND TREATMENT OF GASTRO-ENTERITIS.

Gastro-enteritis is essentially a preventable disease. Hardy[2] pointed out that "the present variations in mortality from diarrhoea in different areas are related chiefly to differences in the rapidity with which these preventable diseases have been controlled".

There is no doubt that gastro-enteritis constitutes an enormous medical and public health problem in this country. The disease is so closely related to malnutrition that the two are almost inseparable. It is important to realise that kwashiorkor represents only a fraction of the total problem of protein-calorie malnutrition.[114,134] The work here presented clearly demonstrates the similarity between severe gastro-enteritis (especially in the older age group) and kwashiorkor. The peak age incidence of kwashiorkor in Cape Town[131] follows closely on that of gastro-enteritis. The morbidity and mortality of malnutrition are only partly reflected in statistics relating to kwashiorkor. They are to a greater extent reflected by the figures on gastro-enteritis.

It is clear that the control of gastro-enteritis as a community problem is essentially dependent on the control of malnutrition and an improvement of the associated social and economic conditions. The most urgent problem is related to infants and young children. Effective programmes of prevention must, however, be carefully planned and will need to vary according to local needs and the populations involved.

Early Diagnosis: Early diagnosis is stressed as an essential part of the effective treatment of gastro-enteritis and malnutrition. Jelliffe et al[114] stressed the need to be able to recognise mild-moderate forms of protein-calorie malnutrition. "From the clinical point of view this is the time to start

preventive treatment. From the public health point of view, it is necessary to know the full dimensions of the problem and its geographical distribution, so that rational methods of prevention can be applied to the most needy areas within a country and their subsequent effects gauged". The value of a low weight for age in this respect has been clearly demonstrated. A variety of weight charts are available in this country.[128,164,165] The applicability of the Boston chart [127] to the local population has been indicated. It is very readily available in a widely-read textbook and is recommended for general use. The late appearance of biochemical[135] and other physical signs of nutritional deficiency stresses the need for a routine assessment of body weight. A low weight for age is probably the most important single sign in the early diagnosis of protein-calorie malnutrition. It is within the reach of every medical practitioner.

Management: Considerable controversy exists on certain aspects of the management of severe gastro-enteritis. Supportive therapy has been fairly well standardised. Bowie[30] recorded a scheme of fluid and electrolyte replacement which is widely used and effective. The tendency to treat all patients alike when it may be important to apply somewhat different principles in malnourished children has been criticised by Gomez and Metcoff et al.[113,151] Their recommendations have not been fully evaluated but deserve further study and attention. Fluid and electrolyte replacement is extremely important and accounts for a striking reduction in mortality.[166]

Most workers are agreed that antibiotics should be routinely used. In their report the MRC antibiotic clinical trials committee[155] demonstrated that more than half the patients made a straightforward recovery without antibiotics but that results were better with treatment. Here it is again important to stress the different reaction of a malnourished child to infection,[102]

and that many severely malnourished children die as a result of infection.[45,90] In the assessment of results different standards are applied and certain groups of cases are often excluded. In the MRC trial[155] shigella and salmonella were excluded. Stein et al[52] excluded "all cases of severe malnutrition" in a series where they reported good results with Chloramphenicol, and criteria of response and relapse were not very clearly defined. These reports indicate the difficulties encountered when attempting to assess and compare results of different studies. The important consideration, however, is not whether many children will recover without antibiotics but that many children die as the resul of an uncontrolled infection. The outcome is unpredictable. This is especially true in malnourished children. Until the reasons for such a difference are more clearly understood, antibiotics must be recommended. The choice of drugs cannot be dictated but again the nutritional status needs consideration in this respect. The use of frequent oral dosage seems sound advice.[102] Judged by the high incidence of Ascaris and giardia in the population there may be a good reason for the routine prescription of piperazine and mepacrine for children over 9 months old attending hospital.

An important aspect to consider in the management of diarrhoeal diseases is the dietary régime prescribed. It is common practice to starve a child with diarrhoea for 24 hours. Thereafter feeding is started with a variety of dilute milk formulae which are confusing even to the initiated. There is evidence that children with malnutrition and diarrhoea can tolerate and adequately absorb full strength milk with or without cream.[162,167] There is thus no reason to confuse the mother with complicated formulae of graded dilutions and unnecessary specification of a particular brand of powdered milk. It is also important to impress upon the mother that starvation is a temporary measure and should not be continued beyond one day. Frequently children with diarrhoea

are kept on dilute and totally inadequate diets for prolonged periods of 2-3 weeks or more.

The frequent occurrence of lactose intolerance in malnourished children[100] complicates the issue of milk feeding. Mothers in this city often complain of a recurrence or worsening of diarrhoea as soon as milk is given. More often than not this is related to skimmed milk in particular. There is experimental evidence that skimmed milk is not more likely than any other milk to precipitate diarrhoea.[167] This is an aspect worth further investigation. It could be that skimmed milk is more frequently incriminated because it is so much more frequently used. Certainly patients do absorb milk protein even if diarrhoea is present and they do usually improve on milk and supportive measures even if it takes several weeks.[35] Without protein they would have no hope of recovery. Children with lactose intolerance respond dramatically to a lactose-free formula. If such a formula becomes easily available it may play a big part in reducing the number of cases with chronic relapsing diarrhoea.

Prevention: Local authorities in South African cities are in general well aware of the problem of malnutrition and an enormous effort is being made towards bettering the situation. Municipal and divisional council clinics are expanding their preventive and therapeutic services. Housing schemes with adequate sewage disposal and water supplies are being undertaken on a large scale and many slum areas have been completely cleared. The Medical Officer of Health in Cape Town indicated the improvement in infant mortality due to these services and the education propaganda by health visitors.[12]

The central government has indicated a further awareness and willingness to tackle the problem. Kwashiorkor has been made a notifiable disease by law and a subsidised milk scheme has been introduced into the bigger centres of the country. However, although kwashiorkor is officially recognised because of the dramatic nature of the disease, the bigger problem of the

underweight child and gastro-enteritis is not generally fully appreciated.

This is a complex and world wide problem.[1] The effects of the disease are most marked in infants and young children of population groups with a low socio-economic standing.[16] It is significant that wellnourished children of economically favoured communities do not suffer from the disease even when they live in essentially the same environment.[9,21]

The relative importance of adverse factors in the home environment of the child often varies from place to place. An adequate assessment of the local needs is therefore always necessary in the planning of preventive services.

Poverty appears to be a major factor particularly in rapidly developing industrial centres where large groups of people are concentrated in bigger cities. Moodie[151] has shown the severe degree of poverty in kwashiorkor families. The present study, conducted in the same area, confirmed a similar situation for gastro-enteritis. Unless the economic standard of the population is raised no lasting improvement can be expected. Assistance such as food subsidies is essential for the moment, but can only be useful as temporary measures.

Poverty never occurs alone. It is associated with ignorance, a poor standard of education, social disorganisation and a lack of proper personal and environmental hygiene.[40,131] Ignorance and social customs are often major factors. Primitive custom does not constitute a major problem in Cape Town where many of the non-White groups have become familiar with the customs of Western civilisation. Jelliffe[16] pointed out that small additional quantities of milk could often be obtained but people use a variety of cereals and sugar, thinking they are suitable food. Williams[168a] similarly indicated that a lack of knowledge of the nutritional needs of the child could be more important than economic poverty. Moodie[131] discussed the common practice in Cape Town of using

squash, other vegetables and black tea, because "it is good for the child". These practices can only be remedied by adequate education. People must not only be taught the relationship between lack of food and disease but must also know the value of one kind of food compared with another. The importance of milk must be particularly stressed. When mothers receive instructions on artificial feeding, these should be simple and clear and in terms that they can understand.

The increased morbidity and mortality from gastro-enteritis in artificially fed infants have been frequently stressed.[16,79,80] The association is especially striking under conditions of poor hygiene. Artificial feeding is widely practised in America, yet there is no major diarrhoea problem.[2,31] In 1912, however, Levy[80] reported a situation which is today still true for Cape Town and many other centres. The morbidity and mortality in bottle fed infants of working mothers were very high. Specific instruction to mothers reduced mortality rates even if they received nothing but advice and encouragement. He said, "we must give every mother the chance to do what we know will solve our problem - to nurse and care intelligently for her own baby". In this present study in Cape Town the first attack of diarrhoea almost invariably followed after the introduction of bottle feeding. Breast feeding should be encouraged whenever possible.

The importance of personal and environmental hygiene in the control of diarrhoea has often been stressed. Schliessman[69] indicated that "the consistant and dramatic decline in diarrhoea morbidity and mortality in the U.S.A. and other countries during the past century has been attributed largely to improvements in environmental hygiene. Adequate sewage disposal gave more dramatic results than water supplies. The proximity of water was apparently more important than the quality of it.[46,169] The failure of individuals and groups

to keep pace with such improvements was stressed by the above authors. This again shows the need for adequate instruction and education regarding these amenities, which are often completely new and strange to the people concerned.

Jelliffe[16] stressed the magnitude of the problem in relation to increasing population and diminishing food supplies. He indicated the need for research into the production and distribution of food and the proper use of available resources. Education of the populace and a general attempt at raising their standard of living might result in a tendency to limit the family size, as experience in Western Europe had suggested.

Adaptation according to local needs is an essential consideration in any programme of diarrhoea control. Williams,[168b] in this context, pointed out the folly of providing preventive but not curative services at welfare centres where the vast majority of children need medical attention. She emphasised the need to adapt hospital management, food supplies, environmental sanitation, etc. to the local problems. She suggested that in maternal and child health services, hospitals should be the centres from which the services radiate to clinics, schools and homes.

These suggestions are singularly applicable to the South African scene. Here curative services are the responsibility of the provincial bodies, while preventive services devolve on the local authorities. The local non-White populace has always accepted illness as inevitable. Steps are only taken to deal with it when it strikes and then they go to receive treatment but no teaching at the overcrowded hospitals. The majority of the most malnourished children have never attended regularly at welfare clinics. This points to the failure of the system as a whole. This failure is recognised in the recent Snyman Commission report,[170] in which the "inherently weak co-ordination" of health services is

condemned. Its first two recommendations deal with the urgent need for an interlinked health service and exploitation of preventive measures.

Health education is at its most effective when allied with therapy. Under the present system these cannot be successfully linked. For the ultimate success of any measures adopted it is necessary to raise the standard of living of the community.

Malnutrition in South Africa is a major, but nevertheless, a soluble problem. A prerequisite is the recognition of its insidious onset and widespread incidence.

## SUMMARY AND CONCLUSIONS.

In the literature reviewed particular emphasis was placed on the association of gastro-enteritis with malnutrition. The poor socio-economic circumstances of the affected population groups were stressed. Diarrhoea morbidity and mortality are particularly high in underdeveloped or rapidly developing countries and the disease occurs mainly in infants and young children. Gastro-enteritis has a multiple aetiology and the cause of the disease is often obscure.

In view of the high incidence of gastro-enteritis in Cape Town a study was undertaken to assess some aspects of the aetiology and the association with malnutrition. The outstanding features of the affected patients were the high incidence and severe degree of malnutrition. Evidence suggestive of enteral infection, such as numerous pus cells in the stools, was commonly found but specific entero-pathogens were less frequently isolated. Intestinal parasites were frequently found in the older malnourished patients. Morbidity and mortality were more closely related to the nutritional status of the children than to any other single factor.

Evidence of nutritional growth failure was strikingly demonstrated by the close correlation between hypo-albuminaemia and a low weight for age. Height/weight ratios of normal and low weight children were assessed. From the growth studies it appears that the American standards for normal weight and height are applicable to the population investigated. The importance of growth failure as a most valuable early sign of malnutrition is stressed.

An investigation of gastric function was undertaken to assess the importance of impaired acid secretion in relation to gastro-enteritis of malnourished children. Acid secretion was impaired in the presence of anaemia rather than in relation to protein-calorie malnutrition. The improvement of

acid secretion after treatment of the anaemia is an important finding. The severity of functional gastro-intestinal changes associated with anaemia stresses the need for prompt treatment of anaemia.

Two chemotherapeutic régimes were compared in the treatment of dehydrating gastro-enteritis. The effectiveness of Chloromycetin palmitate as compared with Penicillin and Sulphadiazine was evaluated. The results were inconclusive, but the advisability of using the inactive fatty acid compound of Chloromycetin in the presence of protein-calorie malnutrition is tentatively questioned.

In the light of recent evidence of lactose intolerance associated with malnutrition, the therapeutic value of a lactose-free formula was studied in patients with gastro-enteritis. It is suggested that a lactose-free milk feed may be valuable in the treatment of chronic relapsing gastro-enteritis.

In conclusion it is suggested that:-

1. Malnutrition is the outstanding feature which determines the course of gastro-enteritis.
2. Enteral infection is the most common precipitating cause of an acute episode of diarrhoea.
3. Treating the infection in gastro-enteritis is important but it is essential also to pay attention to the nutritional deficiencies which are so frequently not recognised.
4. Early detection of malnutrition would prevent the high morbidity and mortality of the disease.
5. Weight deficit is a valuable early sign of malnutrition and an assessment of the weight for age should be an essential part in the examination of any ill child.
6. In the control of gastro-enteritis the emphasis is essentially on prevention.

Where gastro-enteritis constitutes a community problem the disease is associated with malnutrition. Therefore the prevention of malnutrition is an essential step in the prevention of severe gastro-enteritis and vice versa.

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## NITROGEN BALANCE.

The poor absorption of nitrogen in the presence of infection and malnutrition is of particular interest. Although the differences were not significant on statistical analysis, they were fairly constantly present. Nitroge retention was also somewhat lower in the infected malnourished than in the non-infected. It was, however, much higher in these than in the wellnourished children. The poor absorption in the presence of infection may be a factor in the acute nutritional breakdown of chronically malnourished children.

A further interesting finding was the relatively good absorption on a high nitrogen intake. Chung et al[162] reported improved absorption in diarrhoea patients on high intakes even though faecal loss was higher. This work confirms the suggestion that food intake should not be restricted in infantile diarrhoea. This is a very common practice for which doctors are often to blame as much as the ignorant mothers. Prolonged starvation has no advantage and can be distinctly harmful to these patients.

Further studies in this connection seem indicated. So many findings seem to be different between malnourished and adequately nourished children that they cannot be compared. The influence of single factors cannot be assessed in a group of mixed nutritional status. Infection appears to have a different effect on the one compared to the other[154] and metabolism is not always comparable.[163] In experimental studies not enough attention is paid to these differences. Results are considered without allowance for the nutritional status and treatment is prescribed in a similar way.

The Effect of Dehydration on Body Weight and Serum Albumin Concentration.

Loss of weight is an accepted and well-known sign of dehydration. A correction of the weight should be made to allow for this before the body weight is assessed in relation to the age of the patient. It is difficult to lay down rigid criteria for such a correction. In this trial the scheme suggested by Truswell[21] was used. It was interesting to note that the mean weigh gain after rehydration was almost identical to his experience. There was no difference in the weight recorded immediately after rehydration and one day later if there were no clinical signs of dehydration.

In the absence of oedema the actual recorded weight after rehydration is probably the best because it allows for the different degrees of dehydration if previous weightsare not available.

In the presence of oedema an addition of 11% to the dehydrated weight seems a reasonable compromise even if it would overcorrect for some cases.

Truswell's observation on serum albumin concentration in relation to dehydration was confirmed.[21]

In the 2 trials in the out-patient department the 3rd blood sample gave a result which was significantly higher than the 2nd, but still much lower than the first. This may suggest a falsely low value at completion of fluid therapy or it may reflect a degree of dehydration having occurred again between the 2nd and 3rd samples. The body weight suggested that this was unlikely Therefore a redistribution of fluid in the interval between the two samples is more likely to be responsible for the difference in concentration.

On a small number of patients the effect was tested again under hospital supervision during and after therapy in the diet trial. The 2nd sample was lower than the 1st, but after this,for the next 2 days,no significant change