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EPIDEMIOLOGY, CLINICAL FEATURES, AETIOLOGY AND COURSE OF ACUTE INFECTIOUS DIARRHOEA IN INFANTS

by

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Thesis submitted for the
Degree of Doctor of Medicine
University of Cape Town

November 1985

TO: RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL

ABSTRACT

Acute infectious diarrhoea (gastroenteritis) is a major medical and socio-economic problem particularly of the developing world. This study was carried out at the Red Cross War Memorial Children's Hospital in Cape Town where between 4000 and 5000 Black and Coloured children are admitted annually with dehydrating diarrhoea.

The study period was one year from 1st April 1981 to 31st March 1982. The aim was to characterise those infants admitted with dehydrating diarrhoea and the communities from which they originated. The identifiable causes of acute dehydrating diarrhoea, their respective proportions, seasonal pattern and associated clinical picture were to be determined. The relative importance of the aetiological and other associated factors with reference to morbidity and mortality was to be ascertained.

Data was obtained prospectively from a systematically selected non random sample of 545 infants aged 6 weeks to 1 year admitted during the study period. A corresponding group of 297 infants without diarrhoea was studied as a control group. Details of age, race, sex, socio-economic status and background, bodyweight, clinical picture, biochemical and haematological parameters, urine, blood and stool cultures were recorded for each patient. Subsequent course as reflected by a review of the hospital records after an interval of 6 months was documented in each case. In the control group only age, race, sex, bodyweight and identifiable stool enteropathogens were recorded. Data storage, counting and analysis were performed using the Tektronix 4051/4052 computers.

The patient and control groups were of similar nutritional status and age. The patients were generally well nourished and most were admitted with their first diarrhoeal episode. Most presented with acute diarrhoea, vomiting and dehydration. Fever and respiratory tract symptoms were present in a third while metabolic acidosis, hyponatraemia and hyperkalaemia occurred frequently. Hypoalbuminaemia occurred in 27% suggesting that the acute diarrhoeal episode was a severe nutritional insult. Inaccuracies in the clinical assessment of dehydration and metabolic acidosis were identified.

Low birth weight (< 2,5 kg) was common amongst the Coloured infants and this was associated with their being underweight for age at admission.

Both Black and Coloured communities were economically disadvantaged and had substandard living conditions. Coloured parents came from more fixed communities, were younger, more often unmarried, better educated and had smaller families. Black parents came from a largely migrant population, were older, more often married and had larger families. The incidence of breastfeeding was low in both groups but lowest amongst the Coloured mothers.

An hypothesis is advanced that the Coloured infants represent a subgroup at risk in the Coloured community due to parenteral inadequacy. The Black infants are representative of the community as a whole being overwhelmed by negative environmental factors (i.e. massive enteropathogenic load).

Potential pathogens were identified in 66% but regarded as significant after statistical comparison with controls in only 49% of infants studied. Parenteral disease potentially able to cause acute diarrhoea was identified in 23% but considered significant in only 9%. There remained 42% in whom no identifiable cause for the acute diarrhoea could be found. Campylobacter fetus ss jejuni and rotavirus which together were isolated in 31% of patients were the most important enteropathogens identified in this study. Other enteropathogens significantly associated with acute diarrhoea were Shigella, Salmonella group B, Yersinia enterocolitica and enteropathogenic Escherichia coli (EPEC) types 0126:K71 (B16); 0119:K69 (B4); 0127:K68 (B8). Certain enteropathogens varied in pathogenicity during the study period.

The seasonal variation in incidence of enteropathogens did not match the marked summer peak characteristic of the disease in Cape Town. More significant enteropathogens were isolated during the winter months when the incidence of diarrhoeal disease is lowest. During the summer peak large numbers of non significant micro-organisms were isolated from the stool cultures. It is hypothesized that environmental contamination together with other factors as yet unidentified may result in this summer peak.

No characteristic clinical features were associated with specific enteropathogens. Aetiological agents could not be clinically differentiated. Underweight for age, previous episodes of diarrhoea, presence of Campylobacter, Salmonella group B or significant EPEC types and the winter season were shown to be associated with persistence of diarrhoea.

In conclusion this study defines the infants admitted to hospital in Cape Town with acute infectious diarrhoea, the socio-economic characteristics of the communities from which they originate, aetiological factors and factors promoting chronicity of the disease. Arising from the data presented recommendations are made for the more effective prevention, clinical assessment, diagnosis and treatment of acute infectious infantile diarrhoea. Priorities for further research are identified.

ACKNOWLEDGEMENTS

I acknowledge with thanks the contributions of the following departments to the successful completion of this project.

Department of Pathology including Haematology, Bacteriology and Chemical Pathology at the Red Cross War Memorial Children's Hospital, Professor R.O.C. Kaschula.

Department of Virology, University of Cape Town Medical School, Professor J. Moodie.

Gastroenterology Research Laboratory, Institute of Child Health, Red Cross War Memorial Children's Hospital. Professor M D Mann. In particular I am grateful to Miss June Mitchell, Mrs Bartha Fennemore and Mrs Karen Verburg for their meticulous processing of the large number of specimens involved.

Department of Paediatrics and Child Health of the University of Cape Town, Professor H de V Heese.

I am grateful for the support and encouragement received from Professor Malcolm Bowie. Without his wisdom and guidance this project would never have been successfully completed. My thanks are also due to Professor Mike Mann for his criticism and help particularly as regards the analysis of the data.

I am indebted to Mrs Lynore Heuer for her invaluable help with the preparation of the manuscript. I would also like to thank Mrs Hannie van Wyk and Mrs Bettie Fourie for their patience in typing draft after draft without complaint.

The project was funded in part by contributions from the Harry Crosley Foundation and a Medical Research Council grant to Professor M D Bowie.

Finally I am indebted to the nursing staff of the Rehydration Ward or 'Driproom' at the Children's Hospital. In particular I would like to thank the Paediatric Nurse Associates headed by Sister Daphne Hoogenhout for their loyal support and the parents involved in the study for their cooperation.

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INTRODUCTION

Acute infectious infantile diarrhoea (synonyms : infantile gastroenteritis, infantile diarrhoeal disease) is a major problem in the paediatric age group world wide. Together with acute respiratory disease it is the most important cause of preventable deaths in the world.[28] This is particularly so in the developing world where the magnitude of the problem is illustrated by the fact that in 1975 Rohde and Northrup[118] estimated that approximately 500 million cases of paediatric diarrhoea occurred in Asia, Africa and Latin America. With mortality rates conservatively estimated between 1 and 4 percent from 5 to 18 million children die annually of diarrhoeal disease[18]. While the incidence in the developed countries is very much lower, diarrhoea remains a cause of significant morbidity and even mortality[70,135,156].

Predisposing Factors:

Factors such as poverty, overcrowding and poor sanitation are associated with a high frequency of infantile diarrhoeal disease. These factors favour the direct or indirect transmission of diarrhoea causing agents from anus to mouth. Rohde and Northrup[118] state that, 'the incidence of diarrhoea is more closely related to socio-economic conditions than to climate, to poverty rather than place'. This is borne out by the South African experience where acute infectious diarrhoea is a major problem in the Coloured and Black populations while it is an insignificant medical problem in the White population group. South African Whites had an average monthly income of R936 in 1981 compared to R310 for Coloureds and R228 for Blacks[143]. Housing standards of the South African Whites are equivalent to those in any first world country.

In comparison the housing of very many Coloureds and Blacks is as inadequate as that of Third World countries. Southern Africa reflects the world situation in microcosm substantiating the statement of Rohde and Northrup.

Seasonal Variation:

The incidence of acute infectious diarrhoea in Southern Africa shows a marked seasonal variation. During the hot summer months the incidence is high while it is low during the cold winter period[117,118,119,142]. Seasonal variation is well described in reports from many different areas world wide[106]. This seasonal variation has not been adequately explained. It is likely that increasing contamination of foods with bacteria such as Escherichia coli with increasing environmental temperature is an important factor. In the literature there is a tendency to report findings during periods of high incidence when patient material is plentiful. However, if the problem of aetiology and seasonal variation is to be addressed it is necessary for the study to include periods of both high and low incidence. For instance in the developed countries of Europe and North America acute infectious diarrhoea is predominantly a winter disease caused by the rotavirus[14,66,113,153]. In contrast many developing countries have either a summer peak[39,69,117,119,142,144] or year round disease[104,146]. In these areas while rotavirus remains an important cause of acute diarrhoea[66,131,136], bacteria and other aetiological factors play a more significant role.

Aetiology:

A review of the published data concerning the aetiology of acute infectious diarrhoea reveals a large number of patients in whom no pathogenic organism is isolated from stool cultures. Even in more

recent work where stools were tested for the presence of rotavirus there remains in about half of the cases no identifiable agent or factor.

Scrimshaw et al[135] state in Interactions of Nutrition and Infection (WHO Monograph 1968) that 'the major endeavor in basic research on diarrhoeal disease is to distinguish etiological entities, which surely exist'. The position has changed but not dramatically so since 1968. It is also evident from publications that the importance of the various identifiable aetiological agents varies from country to country and from one geographical and climatic area to another within the same country (Table 1,1). These enteropathogens also demonstrate in many instances a year on year variation. For these reasons ongoing research on the aetiology of infectious infantile diarrhoea remains valid.

In Cape Town at the Red Cross War Memorial Children's Hospital (Children's Hospital) between 3 800 and 5 000 Black and Coloured children were admitted annually between 1976 and 1981 with dehydrating diarrhoea (Table 1,2). Acute infectious diarrhoea which is the main cause of dehydrating diarrhoea is consequently a major problem at the Children's Hospital. These children are treated in a specialised short stay rehydration ward. In contrast it is extremely unusual for children from the White population group to require admission to the Children's Hospital for dehydrating diarrhoea. These children are not admitted to the rehydration ward. A comprehensive controlled prospective study of infants with acute infectious diarrhoea has not previously been undertaken in Cape Town. Studies have been published from centres elsewhere in South Africa (mainly the Johannesburg/Pretoria area) and numerous surveys of children with acute infectious diarrhoea in countries worldwide appear in the paediatric literature (Table 1,1). Micro-organisms such as enteropathogenic Escherichia coli (EPEC),

TABLE 1

PUBLISHED SURVEYS

AFRICA

SURVEY	AGES	NO	ROTAVIRUS	CAMPYLOBACTER	SHIGELLA	SALMONELLA	EPEC	OTHERS
			CURRENT STUDY					
SA Blacks/ Coloureds 1981/2 Cape Town	< 1 yr	545 (297)	18,1% (3,9) Elisa	18% (6,4)	5,7% (0,3)	10,8% (7,1)	40,3% (27,2)	Yersinia 0,9% (0)
SA Whites 1960 Johannesburg[116]	< 2 yrs	98 (230)	N D	N D	10% (1)	10% (4)	17% (8)	
SA Blacks 1962 Johannesburg[116]	< 2 yrs	78 (63)	N D	35% (16)				ETEC 19% (10)
SA Blacks 1963 Johannesburg[119]	Most < 2 yrs	310 (221)	N D	N D	W 4,3% (1,9) S 13,4% (1,2)	1% (0) 1,85% (0,6)	43% (23,3)	Nil

( ) = Controls
N D = Not done
E.M. = Electron Microscopy
EPEC = Enteropathogenic Escherichia coli
ETEC = Enterotoxigenic Escherichia coli
CFT = Complement fixation test
IEOP = Immunoelectro-osmophoresis
ELISA = Enzyme-linked immunosorbent assay
W = Winter S = Summer

AFRICA

SURVEY	AGES	NO	ROTAVIRUS	CAMPYLOBACTER	SHIGELLA	SALMONELLA	EPEC	OTHERS
SA Whites 1964 Johannesburg[81]	< 1 yr	90 (169)	N D	N D	2% (0)	10% (3,7)	20% (8,6)	Nil
SA Blacks 1969 Johannesburg[142]	< 3 yrs	131 (128)	N D	N D	19,1% (2,3)	5,3% (2,3)	16% (15,6)	Nil
SA Blacks/ Coloured 1970 Cape Town[155]	Not specified		N D	N D	5%	3,1%	N D	
SA Blacks/ Coloureds 1971 Cape Town[29]	Most < 2 yrs	1191	N D	N D	2,4%	4,5%	12,3%	Giardia 2,9%
SA Blacks 1977 Johannesburg[48]	< 2 yrs	200 (189)	E.M. 14%	N D	8,4% (5,6)	7,9 (5,6)	28,8% (16,9)	Assessed ETEC
SA Blacks 1977 Johannesburg[132]	< 2 yrs	37	49% (CFT) 6% E.M.	N D	5,4%	5,4%	46% 16% sole pathogen	Assessed ETEC 24%

AFRICA

SURVEY	AGES	NO	ROTAVIRUS	CAMPYLOBACTER	SHIGELLA	SALMONELLA	EPEC	OTHERS
SA Whites 1977 Johannesburg[132]	< 18/12	23	61% (winter)	N D	0	4%	High frequency EPEC	
SA Blacks 1979 Johannesburg[82]	0-9 yrs mainly < 1 yr	120 (60)	N D	N D	19% (2)	6% (2)	43% (23)	
SA Blacks 1980 Johannesburg[116]	< 2 yrs	70 (30)	15% (6/41)	9% (0)	17% (3)	43% (17)		
SA Blacks 1979 Johannesburg[16]	< 2 yrs	78 (63)	N D	35% (16)	1% (0)	6% (8)	32% (17)	
	0-8 mths	47 (45)	N D	32% (4)	2% (0)	0% (2)	38% (13)	
	9-24 mths	31 (18)	N D	39% (44)	0% (0)	16% (22)	23% (28)	
Rhodesia 1976[167] Mostly Whites	1032 < 18 mths	2653	31,6% (25)	N D	12%	7%	8%	

AFRICA

SURVEY	AGES	NO	ROTAVIRUS	CAMPYLOBACTER	SHIGELLA	SALMONELLA	EPEC	OTHERS
Ethiopia 1981[146]	81,5% < 2 yrs	962 (199)	27,8% (8) I.E.O.P.	Reported No data	4,4%	0%	5,6%	ETEB (mainly ETEC) 12% Yersinia 1 case
Ethiopia 1982[149]	98% < 2 yrs	175	49% (5) I.E.O.P.	13% (3)	2% (0)	0% (0)	19% (8)	ETEC 9% (7)
Sudan 1969[41]	0-3 yrs 55% < 1 yr	204	N D	N D	8%	5%	17%	
Egypt 1878[1]	< 2 yrs	101	N D	N D	30% (4) (summer)	8% (1)	32% (9)	
The Gambia 1978[121]	1-2½ yrs	32	0% E.M.	N D	---------- Overall bacterial pathogens 12% ----------			

EUROPE

SURVEY	AGES	NO	ROTAVIRUS	CAMPYLOBACTER	SHIGELLA	SALMONELLA	EPEC	OTHERS
Finland 1981[152]	< 1 yr	280	49% E.M. + CFT	2,5%	0%	1,4%	3,9%	ETEC 1,4% Giardia 1,4%
England 1970[70]	< 2 yrs	339	N D	N D	0%	0%	*16,5%	*Specific EPEC Type in 40%
England 1975[23]	< 6 yrs < 1 yr	258 137	N D	38% E.M. 32% E.M.	1,6%	3%	8%	
England 1978[121]	< 2 yrs	67	28,4% E.M.	N D	0%	4,5%	7,5%	
England 1979[87]	Most < 1 yr	150	46% E.M.	3%	5%	6%	0,7%	
England 1980[157]	< 18 months	58 (30)	7% (0) E.M.	N D	0%	3,7% (0)	11% (0)	
Belgium 1973[25]	Uncertain	800 (1000)	N D	5,1% (1,3)	N D	N D	N D	

AMERICA - NORTH AND SOUTH

SURVEY	AGES	NO	ROTAVIRUS	CAMPYLOBACTER	SHIGELLA	SALMONELLA	EPEC	OTHERS
Guatemala 1964[53]	< 1 yr	578 (647)	N D	N D	20,9% (1,5)	0,2% (0,2)	2,9% (4,8)	
Brazil 1975[54]	< 10 yrs	40 (20)	N D	N D	0%	10%	12,5% (0)	ETEC 48% Yersinia) 0% Cholera)
Venezuela 1978[153]	< 5 yrs	293 (66)	41,3% (4,5) E.M.	N D	8% (6)	Not reported		
Mexico 1977[43]	< 3 yrs	62	25,8% E.M.	N D	6,5%	6,5%	13%	ETEC 47%
Mexico 1978[110]	81% < 1 yr	340 (438)	17% E.M.	N D	14%	12%	N D	ETEC 4%
Costa Rica 1978[60]	< 3 yrs	130	38% E.M.	N D	12,3%	10%	21,5%	
Costa Rica 1979[105]	95% < 1 yr	62	40% Elisa	N D	8%	5%	14,5%	

AMERICA - NORTH AND SOUTH

SURVEY	AGES	NO	ROTAVIRUS	CAMPYLOBACTER	SHIGELLA	SALMONELLA	EPEC	OTHERS
Costa Rica 1977/1979[97]	Not given	217	40,3% (5) Elisa + EM	Recently found	N D	N D	N D	Village study ETEC 27-40%
Costa Rica 1982[100] (Rural)	56% < 1 yr	95 (39)	18% Elisa (0)	8,4% (0)	3,1% (0)	0% (0)	Not reported	Giardia 7,2% Cryptosporidium 4,2% (0)
Costa Rica 1982[100] (Urban)	83% < 1 yr	183 (51)	34,4% Elisa (0)	7,1% (0)	0% (0)	0% (0)	Not reported	Giardia 3,1% Cryptosporidium 4,4% (0)
Panama 1982[127]	< 1 yr	94	50% Elisa	N D	3,2%	2%	Not typed	ETEC 2,1%
Canada 1977[56]	87% < 2 yrs	1027	11%	N D	6,5%	1,4%	13,4%	
U.S.A. 1968[102]	< 2 yrs	191 (95)	N D	N D	2% (0)	3%	10% (1)	
U.S.A. 1976[76]	< 2 yrs (most)	143	43% (8) E.M.	N D	N D	N D	N D	

AMERICA - NORTH AND SOUTH

SURVEY	AGES	NO	ROTAVIRUS	CAMPYLOBACTER	SHIGELLA	SALMONELLA	EPEC	OTHERS
U.S.A. 1978[110]	81% < 1 yr	255 (112)	10% (2,8) E.M.	N D	25%	4%	Not typed	ETEC 4%
U.S.A. 1978[60]	< 18 months (most)	57 (23)	28% (4) E.M.	N D	8,8% (0)	0% (0)	19,3% (17)	
U.S.A. 1982[127]	< 1 yr	52	15,4% Elisa	N D	0%	5,8%	Not typed	No ETEC

ASIA

SURVEY	AGES	NO	ROTAVIRUS	CAMPYLOBACTER	SHIGELLA	SALMONELLA	EPEC	OTHERS
Pakistan 1966[68]	< 2 yrs	339 (115)	N D	N D	11,6% (1,3)	0,5% (0,4)	6,7% (3)	
India 1973[144]	< 3 yrs	110	N D	N D	1,8%	0%	10,9%	
India 1977[128]	< 5 yrs	120 (50)	N D	N D	7,4% (2)	0% (0)	17,5% (8)	Cholera 2,5% Giardia 5,8%
India 1977[88]	< 5 yrs	86 (88)	N D	N D	4,5% (2,3)	0% (0)	17,4% (9,1)	Cholera 11,6% Giardia 5,8%
India 1977[88]	< 2 yrs	50 (30)	24% (0) E.M.	N D	4% (0)	6,7% (0)	44% (30)	Cholera 4%
India 1977[88]	< 1 yr	45	26%	N D	6%	8%	50%	
Bangladesh 1981[9]	< 2 yrs	377	11% Elisa	N D	15%	0%	0%	ETEC 20%

ASIA

SURVEY	AGES	NO	ROTAVIRUS	CAMPYLOBACTER	SHIGELLA	SALMONELLA	EPEC	OTHERS
Taiwan 1977[10]	< 4 yrs Most < 1 yr	80 (131)	47% E.M.	N D	0%	3% (0)	Not typed	ETEC 16% No cholera
Thailand 1981[85]	< 6 yrs	105 (90)	36% Elisa	4%	9%	6%	Not typed	ETEC 18% Cholera 2%
Philippines 1978[40]	< 12 yrs Mean 2½ yrs	82 (49)	17% (2) E.M. + Serol	N D	1,2% (0)	6% (0)	Not typed	ETEC 11% (8) Cholera 3,7%
Japan 1978[80]	< 9 yrs Mean 13,8 mths	506	65% E.M.	N D	N D	N D	N D	
Java 1977[136]	< 2 yrs	41	15% (0) E.M.	N D	2% (0)	2% (0)	12% (19)	ETEC 24% 58

TABLE 1,2

ANNUAL ADMISSIONS TO REHYDRATION WARD

YEAR	TOTAL ADMISSIONS
1976	4 957
1977	4 618
1978	3 861
1978	4 504
1980	4 461
1981	5 127

enterotoxigenic Escherichia coli (ETEC), enteroinvasive Escherichia coli (EIEC), non typhoid Salmonellae, Shigellae, Campylobacter fetus ss jejuni, Rotavirus, Yersinia enterocolitica, Cryptosporidium and Vibrio cholerae are recognized as potential causes of acute infectious diarrhoea. These organisms may be carried asymptomatically in the stools particularly in patients from areas where infectious diarrhoea is endemic[135]. To determine the significance of the presence of these potential enteropathogens it is therefore essential to include valid control groups in all aetiological studies. Many of the studies in the literature lack control groups which precludes statistical analysis to determine the significance of these potential enteropathogens in the stool cultures of patients with acute diarrhoea.

Clinical Features:

Acute infectious infantile diarrhoea is a clinical syndrome characterised by diarrhoea and vomiting. Bacterial and viral agents outlined above constitute the major known aetiological factors. Similar symptoms may be caused by infections outside the gut (e.g. otitis media, measles), protein energy malnutrition (kwashiorkor), various forms of food intolerance (cow's milk protein and gluten) and a variety of numerically less important causes. The clinical features associated with the various enteropathogens are summarised in Table 1,3. In most cases these characteristics are unfortunately not sufficiently prominent to enable clinical differentiation of the various infectious agents to be made, particularly in the young child[146]. The mechanisms by which these micro organisms cause diarrhoea are varied (discussed further in Chapter 6) but with a few exceptions the management is similar irrespective of the underlying cause. In many cases the offending micro organism is only identified at a time when the patient has already recovered. In certain situations the clinical picture may suggest a

TABLE 1.3 CLINICAL AND EPIDEMIOLOGICAL FEATURES ASSOCIATED WITH KNOWN ENTEROPATHOGENS[1]

Organisms	Associated Clinical Features		Incubation Period	Epidemiological Features
	Common	Others		
Rotavirus	Vomiting Fever Acute watery diarrhoea	Severe dehydration in some	24-72 hours	Infants and young children. Worldwide in all socio-economic groups. Peak in colder seasons in temperate climates.
Enteropathogenic Escherichia coli (EPEC)[2]	Nausea Vomiting Acute watery diarrhoea	Fever	6-72 hours	Worldwide mainly infants rarely adults. Nursery outbreaks in developed countries
Enterotoxigenic Escherichia coli (ETEC)[2]	Nausea Vomiting Abdominal pain Acute watery diarrhoea	Fever Malaise Severe dehydration	6-72 hours	Infants and young children in developing countries. Traveller's diarrhoea in adults.
Enteroinvasive Escherichia coli (EIEC)[2]	Dysentery-like disease		?36-72 hours	Worldwide. Older children & adults. Sporadic cases and institutional outbreaks.
Campylobacter SS jejuni	Abdominal pain. Fever Malaise Acute watery diarrhoea	Chills Blood and pus in stools	3-5 days	Worldwide distribution. In developed countries may be food-borne or transmitted by handling animals.
Non-typhoid Salmonellae	Nausea Vomiting Fever Chills Abdominal pain Acute watery diarrhoea	Malaise	8-36 hours	Common worldwide. Children. Foodborne outbreaks. Warmer seasons.
Shigellae	Fever Abdominal pain Dysentery	Malaise Vomiting Urgency and spasm with defaecation	36-72 hours	Children. Poor hygiene. Malnutrition. Warmer seasons.
Vibrio cholera	Vomiting Abdominal pain Acute watery diarrhoea	Severe dehydration Circulatory collapse	1-3 days	Children in endemic areas. Adults in newly affected areas.

[1] Table adapted from Diarrhoea Dialogue 1981 Issue 7, 6.

[2] Escherichia coli diarrhoea WHO Scientific Working Group Bull World Health Organ 1980 58, 23-36.

specific enteropathogen. Shigellae in young children for example may produce dysentery associated with a high fever and convulsions[4,77].

In an area where Shigellosis is common these clinical features may justify the early use of antibiotics (Ampicillin or Trimethoprim-Sulfamethoxazole) although in general antibiotics are contra-indicated in patients with acute infectious diarhhoea[207,200]. An awareness of the causes of infectious diarrhoea in a specific area may thus have limited clinical usefulness but is important in the broader sense as regards epidemiology, treatment regimes and preventitive measures.

Motivation for the Study:

For these reasons a prospective controlled study was planned of infants admitted to the rehydration ward at the Children's Hospital. The study was carried out between 1st April 1981 and 31st March 1982 and was limited to infants aged between 6 weeks and 1 year. This age group constitutes the majority of children requiring hospitalisation for this problem. At the Children's Hospital most children admitted to the rehydration ward are under 2 years of age. This is similar to other reports where peak incidence is between 6 months and a year of age[12]. It has been suggested that the frequency of diarrhoeal disease in a community is related to breastfeeding. In societies where children are weaned in the first year of life, the peak of diarrhoea occurs in that year. In areas where weaning is later the peak is around 18 months[99]. The infant group under 1 year has a higher morbidity[9,71] and mortality[97,144] making it especially worthy of more detailed study. A shortcoming of published data is failure to restrict or specify the ages of children in studies. The inclusion of older children in aetiological surveys makes interpretation of the results extremely difficult if not impossible.

This study, the findings of which constitute the basis of this thesis, was further motivated by the fact that a more precise knowledge of the aetiology, epidemiology and clinical features of such a disease at the Children's Hospital could benefit patient care directly. Identification of risk factors in these patients and the communities from which they originate may allow appropriate intervention with reduction of the large number of hospital admissions. Finally clarification of the aetiology and clinical features of acute infectious infantile diarrhoea may indicate further areas for future research.

In a study of this nature with its wide terms of reference it seemed more appropriate to review the published data in conjunction with a discussion of the results obtained. This was done and the appropriate references are included in the discussions of Chapters 4 through 7. There are several general issues concerning the epidemiology, prevention and treatment of acute infectious infantile diarrhoea that will be highlighted in this introductory chapter.

Acute Infectious Diarrhoea and Protein Energy Malnutrition:

The relationship between acute infectious diarrhoea and protein energy malnutrition is of considerable importance[98]. Diarrhoea is a common event preceding protein energy malnutrition in infants of the developing world[30,122]. Frequent episodes of diarrhoea have a strongly negative correlation with growth[95,98] (length and weight). If the possible long term effects of malnutrition on intellectual development[145] are taken into account the problem assumes increased significance. In a study by Al Dabbagh and Ebrahim[3] diarrhoea together with low birth weight and bottle feeding was found to be strongly associated with the development of malnutrition. Black et al[10] reported that malnutrition did not determine the incidence of diarrhoeal episodes but rather the

duration thereof. This is supported by the findings of James[71] that in Costa Rica the incidence of diarrhoea was similar in well nourished and malnourished infants but the duration of diarrhoea was significantly longer in the malnourished group. Cole and Parkin[30] showed physical growth to be severly retarded in an infant population suffering from frequent attacks of gastroenteritis. Many workers feel that infectious diarrhoea is a major precipitating factor in the development of protein energy malnutrition[118,122,135]. Stool losses of nitrogen and fat in well nourished infants with severe diarrhoea (more than 30 gm stoolweight/kg/day) are such that continued nutrient wastage makes enteral nutrition impossible[94]. The role of acute infectious diarrhoea in protein energy malnutrition has significance for the planning of public health measures. Reduction of the attack rates of acute diarrhoea and early termination of diarrhoea will reduce the incidence of malnutrition in the general infant population.

Once protein energy malnutrition is established episodes of diarrhoea are more severe and have a higher associated mortality[97,144]. This together with factors such as inappropriate management, ignorance of the parents and a poor general state of health accounts for a very high mortality rate reaching 20 percent among affected children in the developing world[108]. In contrast mortality rates in the developed countries are reported at a low 1 to 2 percent[70,108].

Strategies for Prevention:

Reduction in the incidence of acute infectious diarrhoea is thus a priority as a measure to combat protein energy malnutrition. Many of the predisposing factors for the high incidence of infectious diarrhoea such as poverty, poor sanitation, unhygienic water supply and inadequate housing are not readily alleviated. They also fall beyond the ambit of

medicine and more in the area of the politician. In general these factors result from the severe socio-economic problems facing the majority of Third World countries. One factor, however, that is closely associated with high attack rates of infectious diarrhoea is potentially correctable. This is the low incidence of breastfeeding which is particularly pronounced in the peri-urban slum populations of underdeveloped countries where infectious diarrhoea occurs in epidemic proportions. In both developed[33,34,70,94] and underdeveloped[49,75,111] areas wholly breastfed infants have a significantly lower incidence of acute infectious diarrhoea[11]. Scrimshaw[135] found the highest rate of acute diarrhoeal disease occurred during the three month period during which breastfeeding was ceasing and the child transferred to a completely independent diet. As already mentioned infants are particularly susceptible to attacks of infectious diarrhoea during the first year of life. It is desirable that breastfeeding should be maintained for as long as possible during this high risk period. This is especially so in areas of high incidence such as the Third World. Early substitution of artifical feeds in these areas where standards of personal hygiene and sanitary practices have lagged behind other cultural changes may have disastrous results. Dietary supplementation is necessary beyond six to nine months of age. At this stage the hygienic preparation of food becomes the critical factor. A purified water supply freely available in the home becomes essential. Unfortunately this is lacking in most developing areas[11].

Recently vaccines against common enteropathogens have become a real possibility. This offers exciting possibilities for the prevention of disease and new developments are reviewed in the Addendum.

Oral Rehydration Therapy (O.R.T.):

It is evident that an immediate removal of these predisposing factors is not possible in most developing countries. In most areas the correction of these factors will be at best a long term objective. It is necessary to consider how the severe nutritional insult of acute infectious diarrhoea can be minimised. It is also imperative that the morbidity and mortality of the disease be restricted to a minimum. In this context oral rehydration in hospitals and at home with an electrolyte sugar solution constitutes one of the major breakthroughs in paediatrics in recent years. Oral rehydration therapy (O.R.T.) initially developed for use in adult cholera patients[64,191,215] has been successfully used for the rehydration of infants with acute infectious diarrhoea throughout the world. Perhaps more important is the prevention of dehydration by the early use of this solution at home at the onset of diarrhoea. That infants can be safely rehydrated orally has been demonstrated beyond doubt[18,63,127,140]. This therapy is based on the cotransport of sodium with glucose (or other sugars) and other actively transported organic compounds by the small intestine. Actively transported monosaccharides (glucose and galactose), neutral aminoacids such as glycine and alanine, and some dipeptides demonstrate an absolute or partial dependence on sodium for absorption. The rate of sodium absorption across the mucosal membrane is in turn considerably increased by the presence of these substrates[64,179]. Oral rehydration solution (O.R.S.) contains sodium and potassium salts plus glucose.

Bicarbonate (sodium hydrogen bicarbonate) has been an additional ingredient to facilitate correction of the metabolic acidosis often accompanying infectious diarrhoea. More recently in an attempt to lengthen the shelf life of O.R.S. the bicarbonate has been substituted by citrate (trisodium citrate dihydrate). This solution has been shown

to be as effective as the solution containing bicarbonate in the management of children with non cholera diarrhoea[164,193,226] (see Addendum). The total osmolarity is kept close to that of plasma and the equivalent of an intravenous infusion is administered via the enteral route.

Ready availability and the simplicity of administration potentially brings the majority of children with diarrhoea within the reach of effective oral fluid therapy. More important in relation to the preceding discussion is the suggestion that O.R.T. may play a positive role in reducing anorexia and promoting intake[64]. Several studies suggest that children on oral rehydration and fed early demonstrate less weight loss on discharge than those managed with intravenous fluids, fasting and a slow return to full oral feeds[5,63,69,106]. This is an important and at this stage controversial finding. If confirmed it provides health workers with a mechanism to break the potentially lethal viscious cycle of diarrhoea and malnutrition. The role of socalled 'super solutions' reported in recent years is reviewed in the Addendum. These solutions offer further reduction of the nutritional insult of diarrhoeal disease. The use of O.R.T. has been widely propagated in both the developed and developing countries. At present a major problem is to develop a community based program capable of reaching the majority of children in the Third World. Minimum requirements of such a program are the chemical ingredients of the O.R.S. together with a means of measuring the ingredients (or a packaged premeasured quantity of ingredients). In addition the educational and supervisory infrastructures are essential to ensure that the children who require O.R.T. in fact receive it in the correct and appropriate fashion.

At present there is still considerable controversy over the concentration of sodium that can be safely administered in O.R.T.[45]. The higher sodium concentration of 90 mmol/ℓ of the World Health Organisation (W.H.O.) solution is ideal for rehydration of malnourished children[63] where the incidence of hyponatraemia is high[125]. It should be borne in mind that the term O.R.S. is inappropriate in many cases as it is used in situations where the aim of the therapy is to prevent dehydration before it occurs or to maintain hydration after an initial period of rehydration. A maintenance solution containing 90 mmol/ℓ may predispose to the development of hypernatraemia particularly in well nourished children from temperate climates[18,124]. It has been suggested that a sodium concentration of 40 to 50 mmol/ℓ may be more appropriate in the maintenance phase[45,140]. Advocates of the single high sodium content solution advise that the child should be encouraged to drink additional water in the maintenance phase to reduce the risk of hypernatraemia[45]. Despite the objections mentioned the WHO solution has been shown to be safe and effective in many studies in both developing and developed areas[63,105,127,232]. Some seeking a compromise advocate the use of an intermediate sodium concentration of 50 to 60 mmol/ℓ[21,195]. The latter has been accepted as a standard O.R.S. for use in South Africa. Potassium is a highly desirable constituent as early correction of potassium deficit results in improved strength, less anorexia and possible long term nutritional benefits[21,105] (see Addendum). The glucose (sugar) concentration should not exceed 2 to 3 percent as there is evidence that a 1:1 molar ratio with sodium is optimal. Higher concentrations lead to increased water and electrolyte losses[45,63,64].

Conclusion:

Finally a quote from the article 'Taking science where diarrhoea is'[118], in which Rhode and Northrup after extensively reviewing the global problem as it was in 1975 concluded that, "Clearly the message is that we who are concerned with the control of paediatric diarrhoea in the world cannot restrict our vision to a single level of research. Instead those working on the delivery end must be constantly alert to potentially useful ideas arising in the laboratory, while the researcher in turn must concern himself with potential practical applications of his work. Together we all have a responsibility to view diarrhoeal disease in a broader ecological context embracing both the micro environment of the host pathogen interaction as well as the macro environment of the man in his society. With continued dedication to workable solutions we will advance further along the journey from scientific laboratory to where the diarrhoea is." Today much research is being done on the problem of paediatric diarrhoea worldwide but in the Third World and particularly in Africa there remains a desparate lack of facilities for scientific investigation where the diarrhoea is. It seems appropriate to reword the oft quoted title to read "Taking the Laboratory to where the diarrhoea is". Is it not time that with improved facilities made available to them that more workers from the areas where the diarrhoea is should decide what is appropriate in their own countries? It is not inappropriate that international bodies and meetings concerned with acute diarrhoea are dominated by workers from North America and Europe? It is hoped that the work presented in this thesis will contribute in some small way to restore the balance.

CHAPTER 2

AIMS AND STUDY DESIGN

The purpose of this study was to obtain data not previously available on infants with acute infectious diarrhoea at the Red Cross War Memorial Children's Hospital (Children's Hospital) in Cape Town. The study was designed in the light of the faults and omissions noted in previously published studies (Table 1.2) as outlined in Chapter 1. In particular, note was taken of the general lack of adequate comparative control data and the often imprecise data relating to the ages of children studied.

2.1 AIMS

The aims of this study were the following:

i. To characterise those infants admitted to the rehydration ward at the Children's Hospital with acute dehydrating diarrhoea.

ii. To define within the constraints of a hospital based study the communities from which they originate.

iii. To determine the identifiable causes of acute dehydrating diarrhoea and as a subgroup thereof the identifiable causes of acute infectious diarrhoea in dehydrated infants admitted to the rehydration ward.

iv. To determine the proportions, seasonal pattern and clinical picture associated with each of the respective causes.

v. To determine the relative importance of the various aetiological and other associated factors with particular reference to mortality and morbidity.

2.2 STUDY DESIGN

The study was undertaken in the outpatients' department of the Children's Hospital. A brief description of the normal progress of patients through the outpatients' department is given to clarify further discussion of the study design. Patients arriving at the Children's Hospital are initially registered at the reception desk (Figure 2.1 : (1)). After waiting in the reception area (2) while the hospital file is drawn and the child is weighed (3), they are sent through to the outpatient consulting area (4). At this point the files are distributed in the chronological order of arrival to the duty medical officers (5). If deemed necessary the patient is referred (6) either to the rehydration ward in the case of dehydrating diarrhoea (7P) or to the paediatric registrar for further evaluation (7C). In the rehydration ward the patient is evaluated, necessary investigations performed and treatment commenced. Patients considered by the paediatric registrar to require hospital admission for conditions other than dehydrating diarrhoea are admitted to the short-stay emergency ward (8).

Infants selected for inclusion in the study were those admitted to the rehydration ward. To enable the seasonal trends to be determined the study was planned over a period of one year. The total number of patients admitted during this period (4000 - 5000) was too large to permit the inclusion of every patient meeting the study criteria. The study was designed to provide a minimum 15 percent sample of the total admissions between the ages 6 weeks and one year. The first 3 patients admitted between 07h00 - 15h00 meeting the criteria for inclusion were studied on weekdays only. A majority of admissions to the rehydration ward daily occurred during this period, This method of sampling provided a manageable number of patients enabling rapid specimen collection and handling.

A true random sample based on random numbers would have been ideal but considerations such as general patient care, clinical assessment for the trial and sample collection made this impractical. A systematically selected non random sample[27] was thus taken. In view of the haphazard nature of the children's arrival at the outpatients department, progress through the various

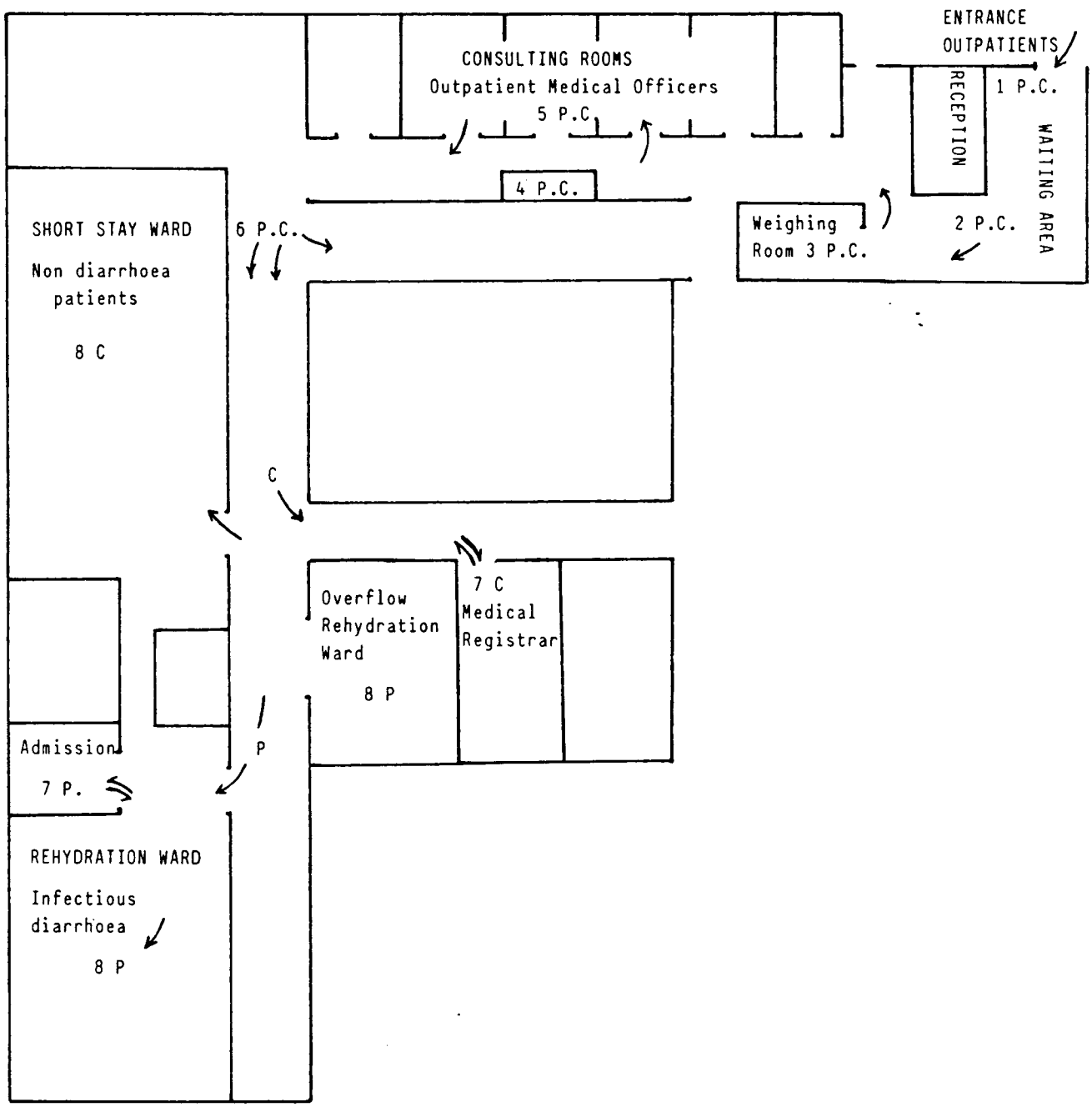


Figure 2,1 Schematic Diagram of Outpatients Department Children's Hospital

P = patients

C = controls

outpatient areas and final referral to the rehydration ward, the sample was considered representative of the total admitted to the rehydration ward.

Controls were matched for age and nutritional status. The control infants without diarrhoea were either those admitted to the short stay emergency ward or those seen in the outpatients department during the same 24 hour period. Control infants were considered of utmost importance in a study of this nature. The mere presence of a known enteropathogen in a stool culture does not necessarily indicate that this organism is the aetiological agent in the infant concerned. Asymptomatic stool carriage of these potential enteropathogens is well recognized[52,116,149]. The inclusion of controls allows for comparison and comment on the statistical significance of the presence of potential enteropathogens in the stools of infants with acute dehydrating diarrhoea.

All patients with the exception of 28 infants and all controls were selected and assessed by the author on admission. The 28 infants in the patient group not examined by the author were examined by an advanced paediatric clinical sister whose competence was confirmed by the author. Patients were then seen daily thereafter by the author until discharge or transfer from the rehydration ward. This served to standardise the clinical examination and make any subjective bias in the clinical assessment a constant factor.

To assess the longer term outcome the hospital files of all patients were reviewed after a period of not less than 6 months after discharge. In addition all patients are routinely visited at home after discharge from the rehydration ward by a community health sister to assess the child's progress and home circumstances. This cannot be done in those patients whose parents furnish incorrect addresses or have no fixed abode. These reports are returned to the hospital files and together with clinical notes from subsequent hospital visits constituted the limit of follow-up for this hospital based study. The review was carried out to determine later mortality and morbidity resulting from the initial acute diarrhoeal episode.

The study reflects a representative sample of infants hospitalised with acute dehydrating diarrhoea and a comparable group of infants from a similar hospital environment without diarrhoea. The shortcomings of the survey being solely hospital based are recognized. The aims and conclusions must therefore be limited to the hospital population studied. The situation in the communities from which these infants originate can only be indirectly inferred. No firm conclusions can be drawn from this study as to, for instance, the seasonal pattern or relative importance of the identifiable causes of acute infectious diarrhoea in the wider Cape Town area.

CHAPTER 3

CLINICAL MATERIAL AND METHODS

For the period of one year from 1st April 1981 to 31st March 1982, a survey of infants with acute dehydrating darrhoea was undertaken at the Red Cross War Memorial Children's Hospital. Children presenting with dehydrating diarrhoea are admitted to a specific ward at the Children's Hospital for resuscitation and intravenous rehydration. The latter is required in the majority of cases. Once rehydrated and able to maintain hydration without intravenous fluids they are discharged although the diarrhoea may still be present. Thereafter follow-up is either at a local "day" hospital or in the outpatient department of the Children's Hospital. If the child is unable to maintain hydration without intravenous fluids after 72 hours transfer is arranged to a conventional ward at the Children's Hospital or at one of the associated group of peripheral hospitals for further management. During the child's stay in the rehydration ward a parent or an escort is required to remain with the child to provide basic nursing care.

3.1. PATIENTS : CRITERIA FOR SELECTION

The infants with acute dehydrating diarrhoea in the sample studied were those aged 6 weeks to 1 year admitted to the rehydration ward between 06h00 and 15h00 on weekdays (Mondays to Friday inclusive). A maximum of 3 patients per day taken in chronological order of admission were included in the study. Not more than 15 patients were studied in any week. The patient group consisted of 545 infants.

3.2. ACQUISITION OF PATIENT DATA

Parents (in the majority the mother) or escorts were questioned regarding the current illness, past medical history, feeding practices and the families socio-economic status. These data were obtained using a standard questionnaire (Annexure A). All information was elicited by the author for each patient included in the study. The bodyweight and axillary temperature was recorded for each patient on admission. A thorough physical examination was performed on the majority (517) by the author and in the remainder (28) this was done by an advanced paediatric clinical sister of established competence. The degree of dehydration, acidosis and presence of shock was assessed clinically.

3.3. COURSE AND OUTCOME

Patients were reviewed daily by the author until discharge home or transfer to another ward. The rehydrated weight or discharge weight (the latter in infants transferred to other wards with dehydration still present) was recorded. Subsequent hospital records were reviewed at an interval of not less than 6 months to assess long term outcome with special reference to recurrence of diarrhoea.

The patient group consisted of 545 patients, which was a 17,2 percent sample of the 3163 infants aged 6 weeks to one year admitted to the rehydration ward with diarrhoea, during the year of study.

3.4. CONTROLS : CRITERIA FOR SELECTION

Control infants were matched for age and selected mainly from infants admitted to the short stay "emergency ward" at the Children's Hospital for conditions other than diarrhoea. Most of these infants had infections of the respiratory tract or central nervous system. The remainder of the control group attended the paediatric outpatient department for minor ailments. None of the controls gave a history of diarrhoea in the preceding month. Stool specimens were collected between 07h00 and 15h00 on weekdays. A maximum of 10 controls was included in the study in any week.

The stool specimens from the control group were inspected by the author and a control infant was included only if the stool was "within normal limits". A stool not readily taking the shape of the container in which it was collected and with no other abnormal features such as blood and significant amounts of mucus was accepted as within normal limits.

The control group consisted of 297 infants.

3.5. SPECIMEN COLLECTION

3.5.1. Stools

Fresh stool specimens were collected in sterile containers from patients and controls. Stools were either passed spontaneously or defaecation was induced by the gentle passage of a gloved

finger into the rectum. All specimens were transported to the laboratory within an hour of collection.

3.5.2. Urine

Urine specimens were obtained by bag collection in the majority of patients. Urine collection was precluded in some due to a severly excoriated perineum. In others, often female infants, the urine was discarded due to faecal contamination.

3.5.3. Other specimens

Blood samples were taken from the patients on admission for acid-base and electrolyte estimation, a full blood count, differential white cell count and blood culture. Blood culture bottles were prewarmed in an incubator before use. In addition a sample of plasma was stored at -20°C for later estimation of serum proteins. Further investigations (such as chest radiographs, lumbar punctures, and further chemical tests) were performed by the routine laboratories at the request of the ward medical staff, as clinically indicated.

3.6. LABORATORY PROCEDURES

3.6.1. Bacteriology

All stool specimens were processed in a research laboratory by the same medical technologist (J.M.). The appearance of the stool was noted and all specimens were examined microscopically

shortly after arrival in the laboratory for white cells, erythrocytes and intestinal parasites.

All stool specimens were plated onto MacConkey and Salmonella-Shigella agar and cultured in Tetrathionate broth.

After 24 hours the Tetrathionate broth was subcultured onto Salmonella-Shigella agar. Standard bacteriological procedures were used to isolate and identify Salmonella, Shigella, Escherichia coli and Yersinia enterocolitica[31]. Stool specimens were cultured separately for Campylobacter fetus ss jejuni using a modification of Skirrow's method[141]. (Burchell B, Roux E, personal communication Annexure B). All cultures for Campylobacter were performed in the routine bacteriology laboratory.

Escherichia coli agglutinating rapidly with grouping sera types (Wellcome Research Laboratories) 018c:K77(b21); 026:K60(B6); 044:K74(L); 055:K59(B5); 086:K61(B7); 0111:K58 (B4); 0112:K66(B11); 0114:K90(B); 0119:K69(B14); 0124:K72(B17); 0125:K70(B15); 0126:K63(B8); 0128:K67(B12); 0142:K86(B);, were designated enteropathogenic Escherichia coli. (E.P.E.C.).

Enterotoxin production by the gram negative bacteria and entero invasion was not assessed. Acid fast staining for Cryptosporidium was not performed.

3.6.2. Virology

An aliquot of stool was mixed with viral transport medium (Annexure C). The supernatant, after the mixture had been centrifuged at 10,000 G, was stored at -20°C. The specimens were subsequently tested in batches. The presence of rotavirus was detected by the ELISA technique using a commercially available kit (Rotazyme^{R}, Abbott laboratories).

3.6.3. Blood and Urine Culture

Blood culture and urine specimens were examined and cultured by standard techniques in the routine bacteriology laboratory.

3.6.4. Biochemistry

Total serum proteins were measured using the Biuret method read with a Beckman Model 125 Spectrophotometer[74]. An Electrophoretic method[74] was used to determine serum albumin levels and read by a Gelman ACD 15 densitometer. Estimations were performed on batches of stored plasma.

Acid-base estimations were done on an ABL2 laboratory (Radiometer Copenhagen) and electrolytes measured on a flame Photometer 243 (Instrumentation Laboratory). A Coulter Counter Model 5-Plus was used for full blood counts. Differential counts were obtained from smears stained using a May-Grunwald-Giemsa Stain.

Total serum protein and albumin estimations were done in a research laboratory while all other investigations were performed in the routine laboratories at the Children's Hospital.

3.7. DATA STORAGE AND ANALYSIS

Patient data was initially recorded on individual data sheets. After the hopsital records had been examined, the data of each patient was stored in summarised form on magnetic tape using a Tektronix 4051/4052 computer. The control data was stored in a similar fashion. All data entry and analysis was performed by the author. Further counting and analysis was undertaken using the computer.

Standard methods of statistical analysis[37,139] were employed and the specific test is designated in the relevant text.

CHAPTER 4

SOCIOECONOMIC AND DEMOGRAPHIC DATA

The socioeconomic status and other characteristics of the community from which the patients came were obtained by history. Similar information was not obtained from the control group. The patients were from two different ethnic groups, the Black or negroid and the Coloured or mixed group. The Blacks orginate mostly from Transkei and Ciskei, two semi-autonomous states situated about 1 300 kilometers from Cape Town (Figure 4.1). The majority come from the Republic of Transkei with their parents who arrive in the Western Cape as migrant workers. A lesser number of the infants are brought to Cape Town specifically for medical attention. Blacks in the Cape Town urban area were estimated to constitute 12,6 percent of the total population of 1458620 in the 1980 census[143]. The Coloured population is indigenous to the Western Cape and are defined as persons of mixed racial origins not belonging to the racial groupings black, white or asiatic[103]. Nevertheless the Cape Coloureds are a relatively well defined population group living within the boundaries of greater Cape Town and also elsewhere in the Western Cape (Figure 4.2). On average they are at a higher socioeconomic level than the Black population. In the 1980 census the Coloured community was estimated to form 53 percent of the population of greater Cape Town[143].

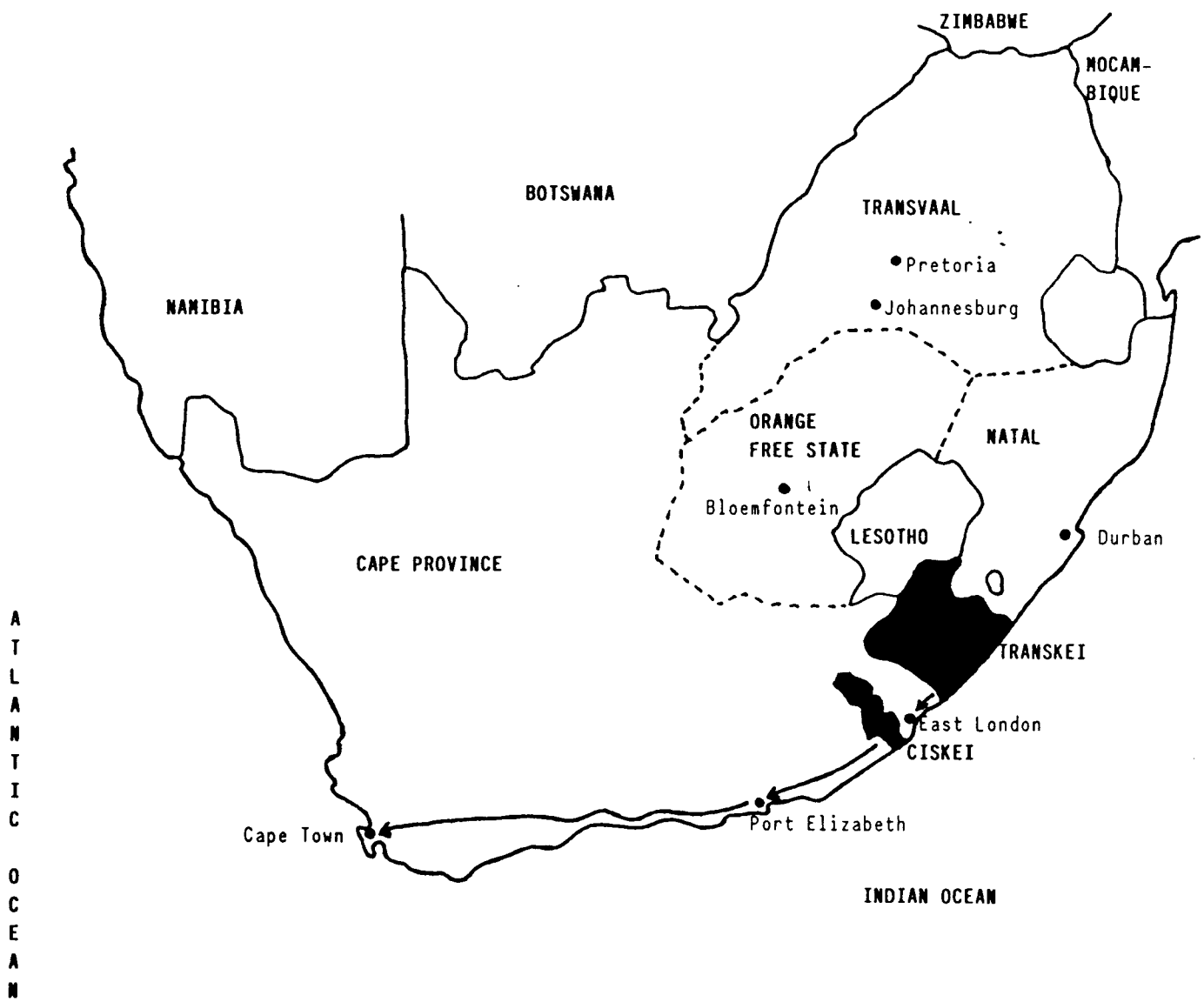


Figure 4.1 Map of South Africa

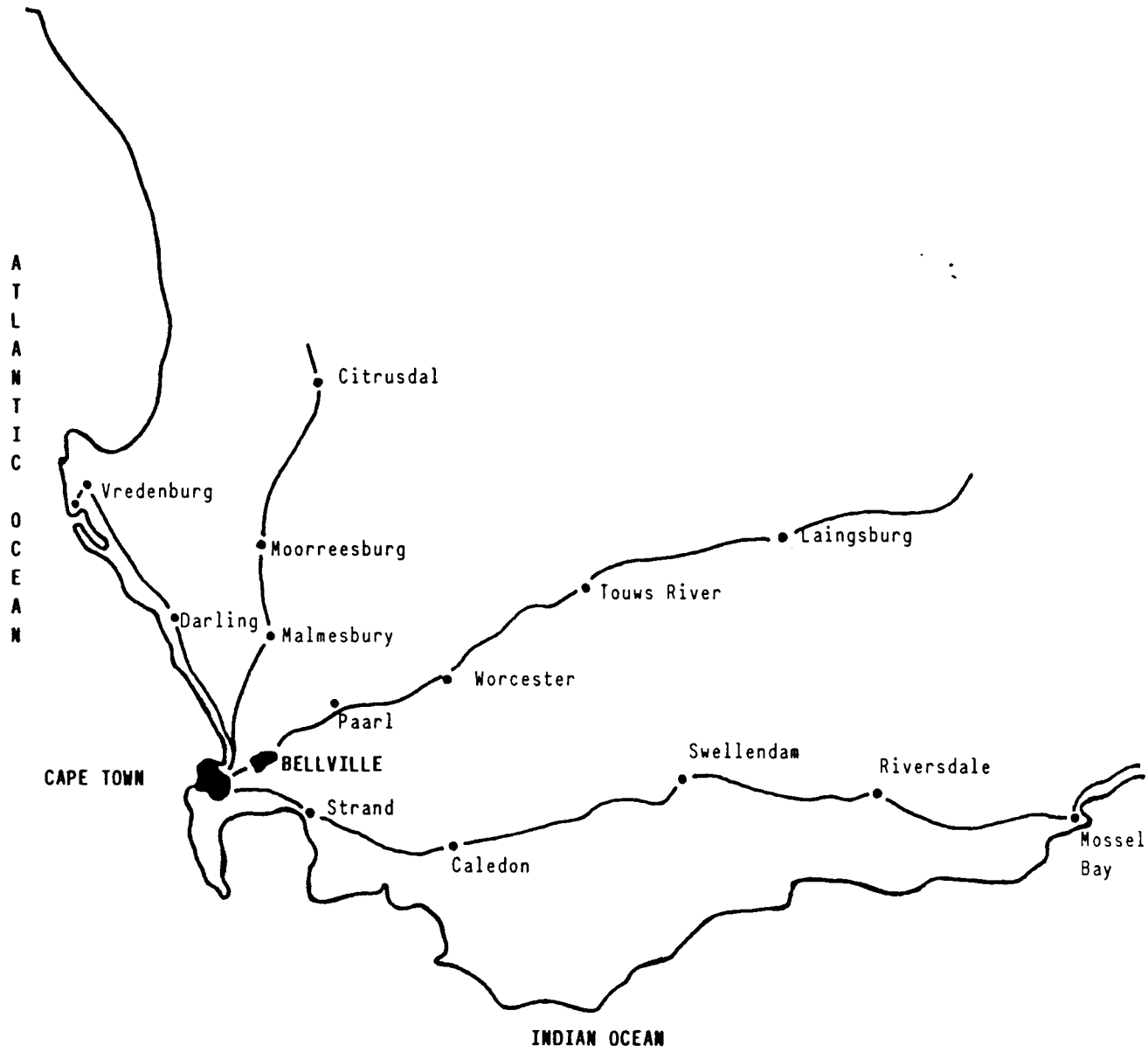


Figure 4.2 Map of Western Cape

RESULTS:

4.1. BIRTH DETAILS

4.1.1. Type and place of birth

The majority of infants were born either in hospital (61,1 percent) or in a local midwife obstetric unit (M.O.U.) or clinic (25,6 percent). The remainder (13,3 percent) were born at home (Figure 4,3). Most were uncomplicated vertex deliveries (84,1 percent) and only in a minority was birth either by caesarian section (10,7 percent) or otherwise complicated (in most instances breech deliveries) (5,2 percent). A comparison between the Black and Coloured infants (Figure 4.4) shows that the incidence of normal vertex deliveries is similar (81,2 percent Blacks vs 88,2 persent Coloured). More caesarian sections were performed in the black group (X^2 test $p < 0.001$). Infants born at home were a minority with only 71 such deliveries and significantly more of these were black infants (X^2 test $p < 0.001$). In contrast more Coloured infants were born in the M.O.U.'s (X^2 $p < 0,005$). There was no significant difference between the numbers of each group born in hospital.

4.1.2. Birthweight

The birthweights of 400 infants (73,4 percent of the total) were recorded and are shown in Figure 4.5. Most were within the normal range with only 67 (16,5 percent) below the accepted lower limit of 2,5 kgm[7]. Significantly more Coloured infants

Figure 4.3 PLACE OF DELIVERY

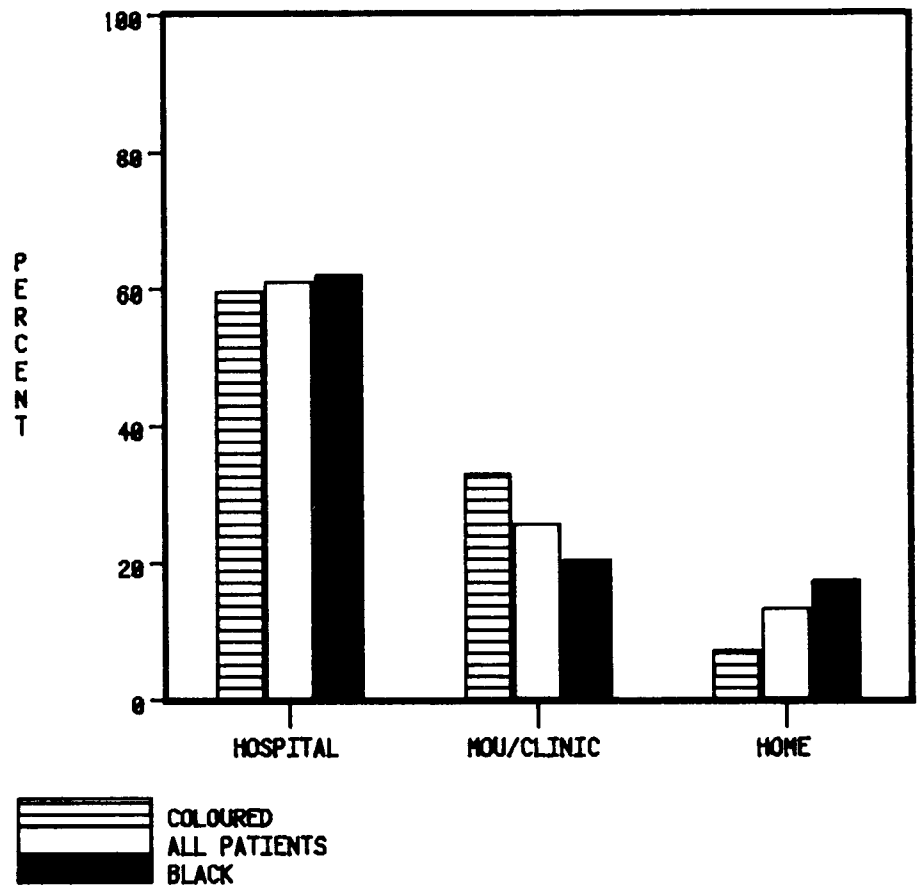
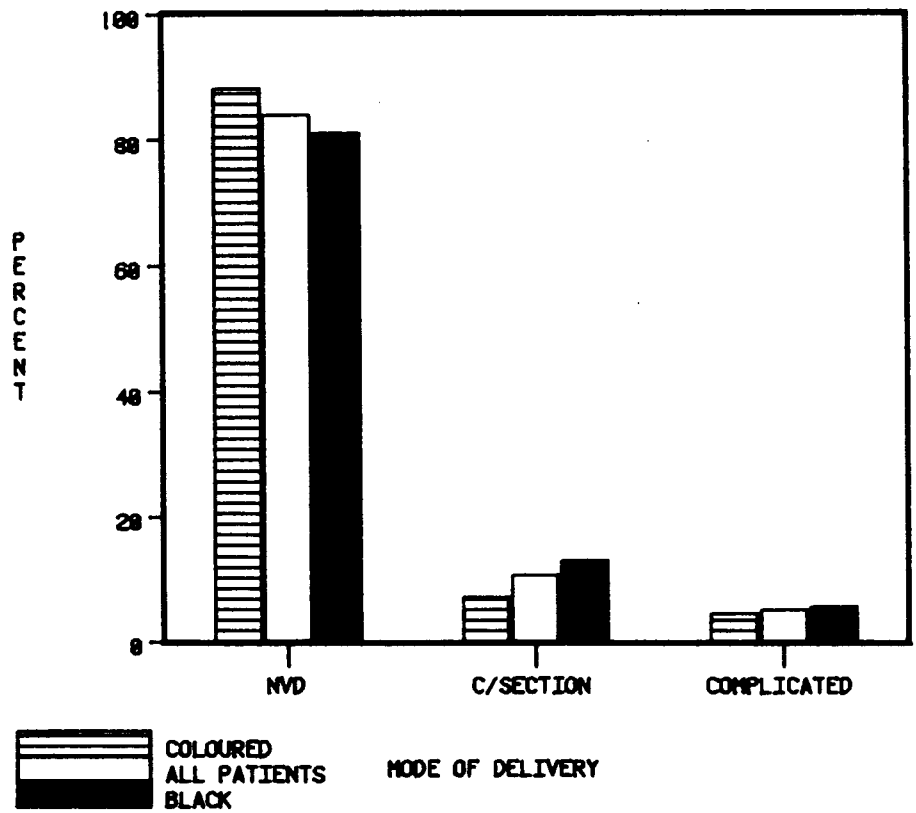


Figure 4.4 MODE OF DELIVERY



(24,6 percent) were under 2,5 kgm than Blacks (X^2 test $p < 0,0002$).

4.2. INFANT FEEDING PRACTICES

In 539 patients an adequate history of the feeding practices prior to admission to the rehydration ward was obtained. History taking was directed particularly at the incidence of breast or artificial feeding and the introduction of solids. Breast feeding had never been established in 105 patients (19,5 percent). Two hundred and sixty nine infants (49,9 percent) had been fully weaned at the time of admission. The remainder (30,6 percent) were breast fed on inclusion into the study. A majority of those weaned on admission were over 6 months of age (65 percent) differing from those still receiving breast milk where the majority were under 6 months of age (60 percent). Only 2 infants both under 6 months were exclusively breast fed.

A majority of the infants (84 percent) were receiving solid feeds (food other than milk) prior to admission. Almost all infants (90,5 percent) over 6 months of age were receiving significant amounts of solids, either as cereals or an appropriately prepared (homogenised) mixed feed from the meals eaten by the family. Under 6 months of age, 44 percent were receiving occasional solid feeds in the form of commercially available baby cereals (Nestum, Cerelac). A further 28 percent ingested significant amounts of solid feeds and the remainder received solely milk feeds.

Figure 4.5 BIRTHWEIGHT

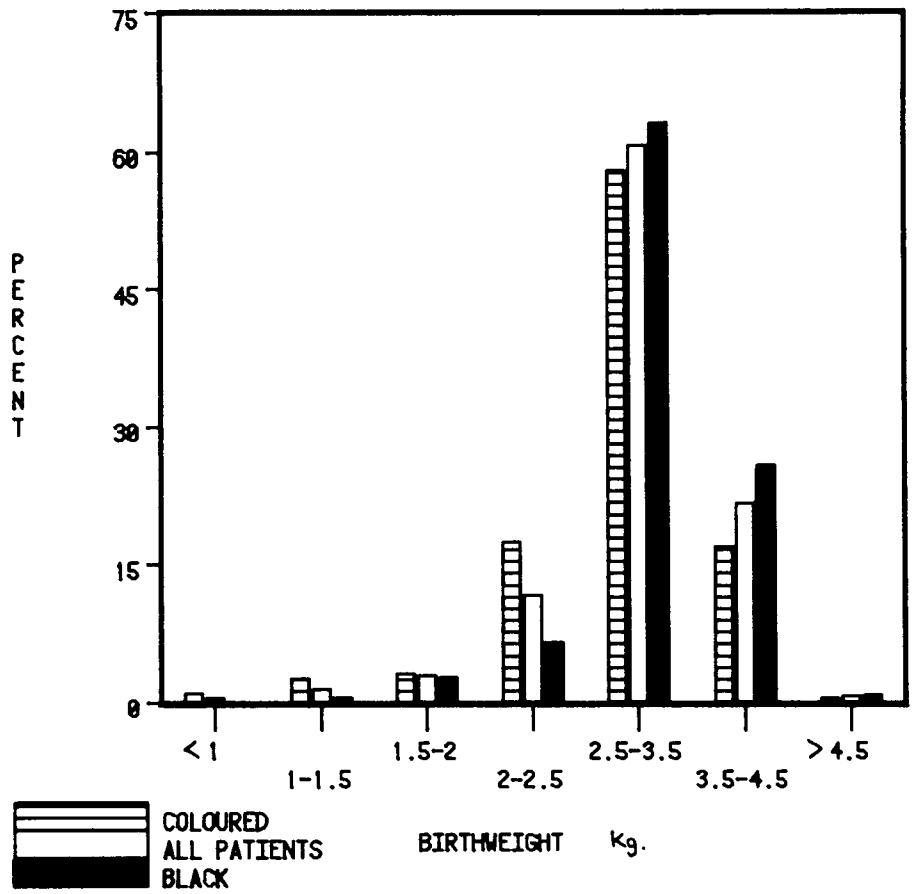
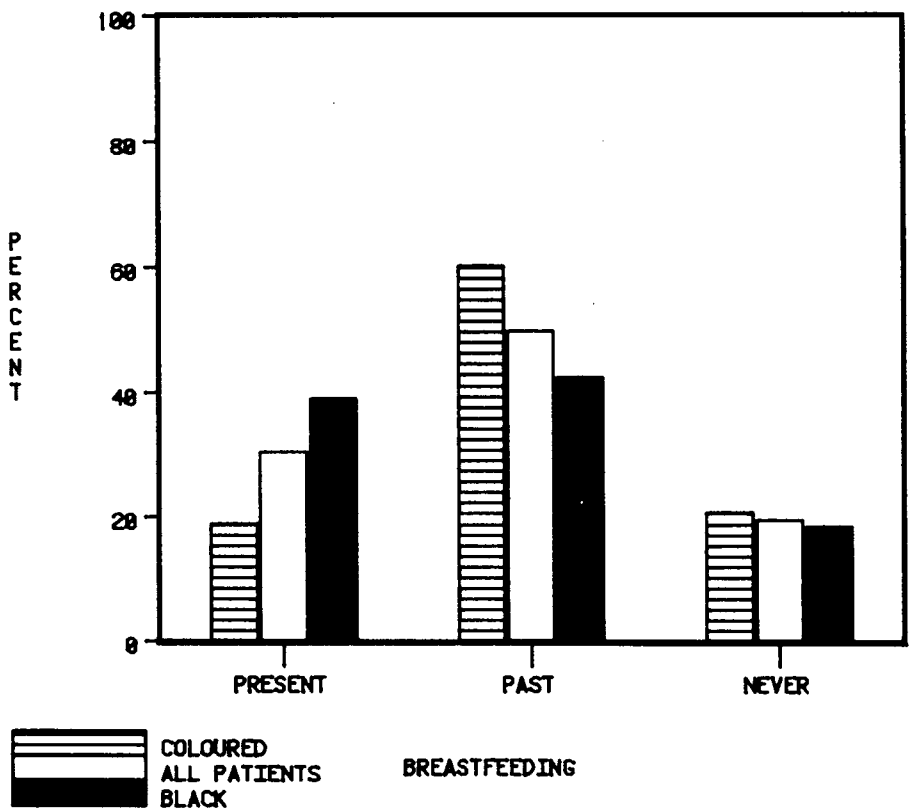


Figure 4.6 FEEDING PRACTICES



The duration of breast feeding was ascertained in 426 infants who were accompanied by a parent or close relative. In this group, 261 (61,3 percent) were breast fed for 3 months or less. Excluding those infants who were younger than 3 months at the time of inclusion into the study 48 percent were breast fed for more than 3 months but very few were breast fed for over 6 months (18 percent).

Analysis of the incidence of breast feeding in the two racial groups (Figure 4.6) reveals no difference in the number of infants never breast fed (X^2 test $p = 0,06$). More Coloured infants had been weaned on admission to the rehydration ward than Black children (60,2 percent vs 42,5 percent) and this difference was statistically significant (X^2 test $p < 0,0001$). More Black infants were breast fed (X^2 test $p < 0,0001$).

4.3. FAMILY BACKGROUND:

4.3.1. Parental age

The mother's birthdate was known in 526, and the fathers age in 419 instances. The mean age of the mothers was 25,5 years. Almost three quarters (72,5 percent) of them were under 30 years of age while 59,5 percent were aged from 20-30 years. Twenty six mothers (5 percent) were under 18 years of age. The fathers were on average older (mean age 30,1 years) with 30 percent aged 30-40 years and only 4,5 percent under 20 years. The parental ages are summarised in Figures 4.7A and 4.7B. Comparison of

Figure 4.7A MATERNAL AGE RANGE

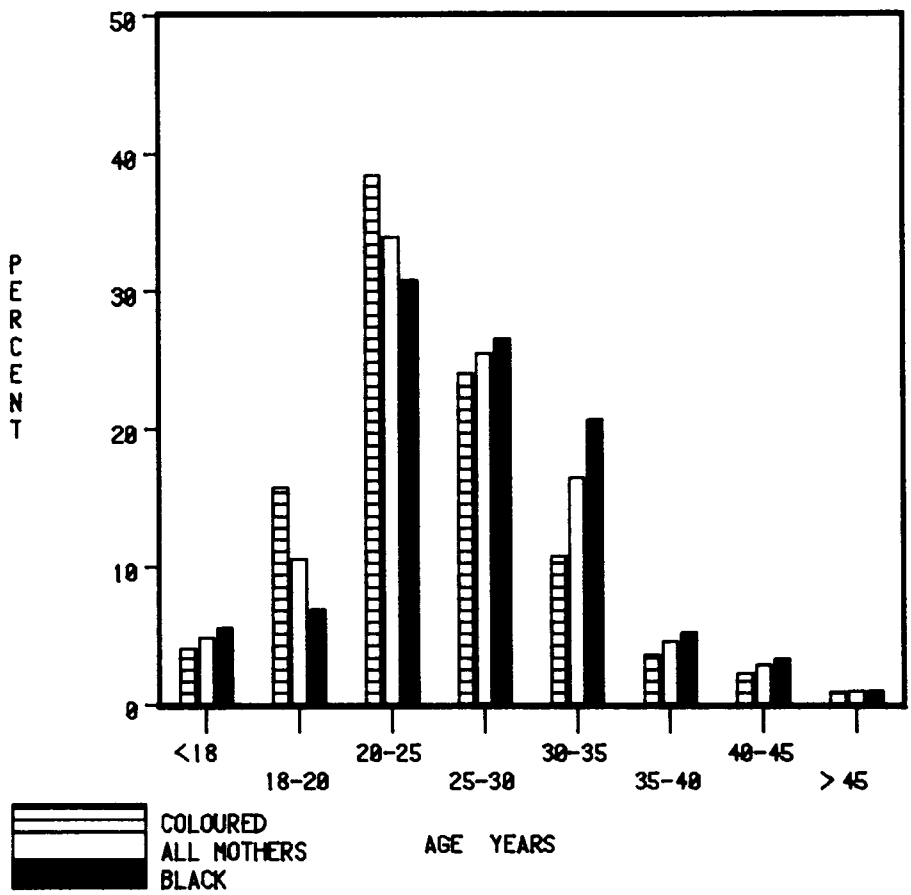
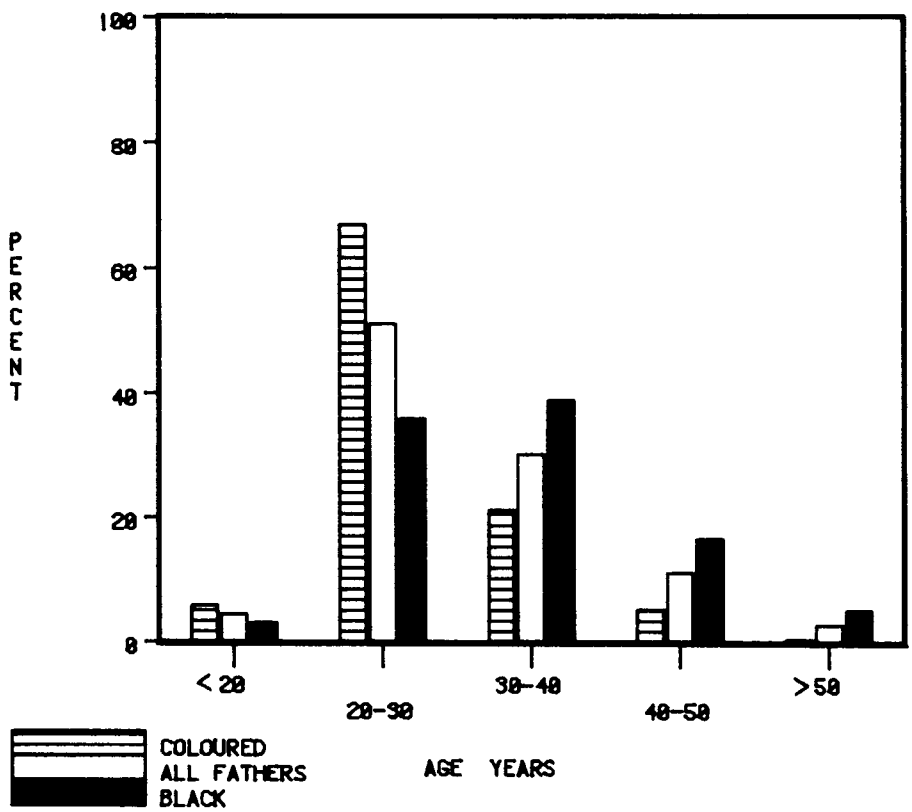


Figure 4.7B PATERNAL AGE RANGE



parental ages shows that the Coloured parents were younger than their Black counterparts.

4.3.2. Mother's educational level

This was known in 514 mothers. Ninety one (17,7 percent) had received no formal education (termed as illiterate), 43 (8,4 percent) had attended school for 3 years or less (termed semiliterate) and the remainder had received enough education to be classed as literate[113]. Of these, 44 percent (of the 514) had received some primary education (Standards 2-5), 19,4 percent had achieved junior secondary level (Standards 6-8, but not obtained a Junior Certificate or Standard 8 pass) and 8,3 percent reached the secondary level (Standard 8 or higher). Only 3 mothers (0,6 percent) had completed their secondary education with a matriculation or school-leaving certificate.

Comparison of the levels of education of the Black and Coloured mothers shows that significantly more Black mothers had received no education at all (X^2 test $p < 0,001$). In contrast the Coloured mothers were more frequently educated to the primary or junior secondary level. Only a small number of mothers had achieved a secondary school education. There was no difference in the frequency of secondary school education between the two groups. The differences between the two racial groups was caused by differences at the lower standards of education. The educational levels of the whole group and the two subgroups are shown by Figure 4.8.

Figure 4.8 MATERNAL EDUCATION LEVEL

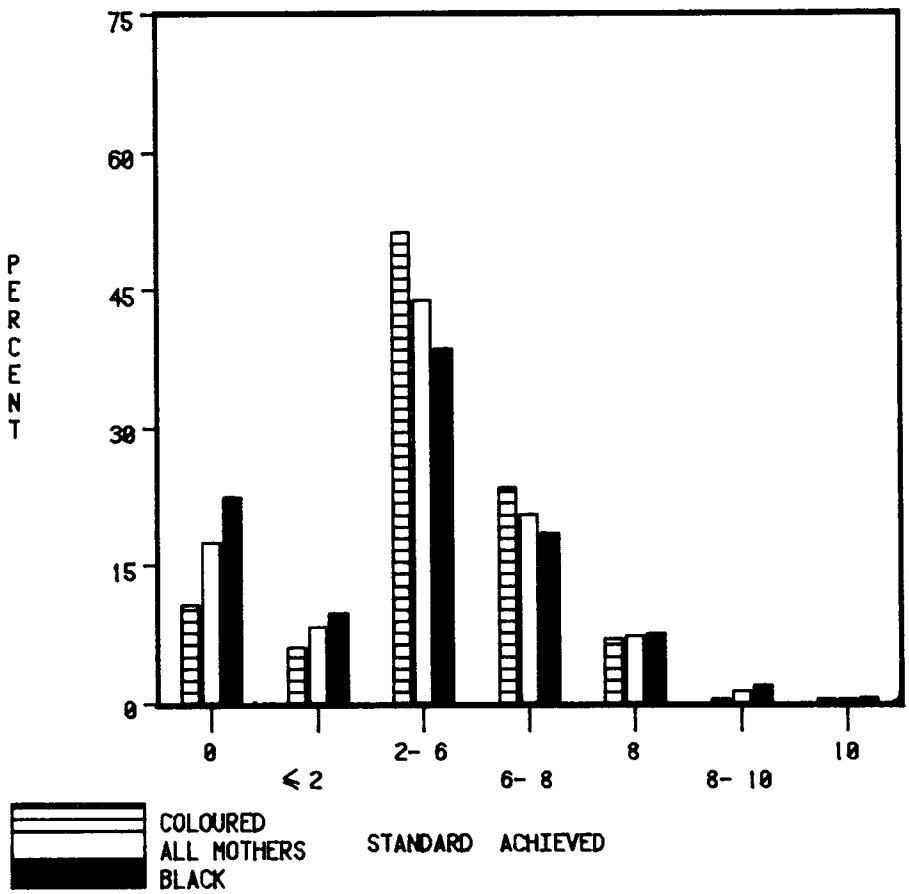
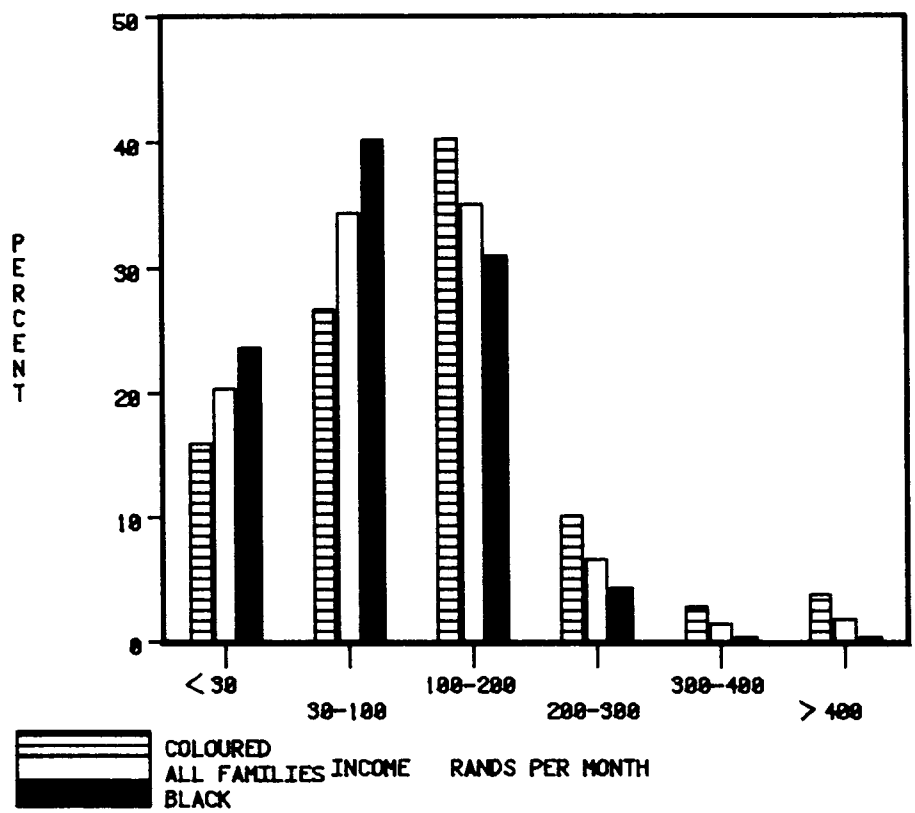


Figure 4.9 FAMILY INCOME



4.3.3. Marital status

In 535 cases the marital status was known. Of this total equal numbers were married (50,7 percent) and unmarried (49,0 percent) with only 2 Coloured couples divorced. Fewer Coloured couples (43,6 percent) were married than Black parents (55,9 percent) and this difference was significant (X^2 test $p < 0,01$).

4.3.4. Employment

Overall 79,6 percent of the families had one parent employed full-time. Amongst Coloured families, 84,1 percent had one adult employed, while in the Black group the figure was lower (77 percent). In both groups, the father was the sole breadwinner in the majority (Coloured 88,6 percent of fathers sole breadwinner vs Blacks 95,4 percent). Black fathers were mostly employed as unskilled and semi-skilled manual labourers in the construction and allied industries, while the Coloured men were more frequently in semi-skilled or to a lesser extent skilled employment. Of the small number of mothers employed, most were either domestic servants (Blacks) or factory workers (Coloureds). Table 4.1 shows the marital status and employment of the parents.

4.3.5. Family income

This information was obtained from the mothers in most cases and was uncorroborated data. This data has certain limitations. Many of the Black mothers were unsure of the family income or

TABLE 4.1

MARITAL STATUS AND EMPLOYMENT

EMPLOYMENT OF PARENTS		MARITAL STATUS			
	N = 533	BLACK N = 313		COLOURED N = 220	
		Married	Unmarried	Married	Ummarried
Parents Unemployed	103 (19,3%)	18 (5,8%)	52 (16,6%)	6 (2,6%)	27 (12,3%)
Father Employed (full time)	395 (74,1%)	151 (48,2%)	80 (26,6%)	79 (36%)	85 (38,6%)
Father Employed (casual)	6 (1,1%)	2	2	1	1
Mother Employed (full time)	9 (1,7%)	0	3	2	4
Both	20 (3,8%)	4	1	8	7

were given food and other goods directly by the father and were unaware of their value. It may at best serve to indicate the range of income for the populations from which the patients originated. In 69 families (23 Coloured, 46 Black) an estimate of the income was not possible as either the infant was not escorted by a parent or the mother could give no estimate of the family income. In the remaining 476 families (87,3 percent) the income pattern was as shown in Figure 4.9. Roughly equal percentages of the Black and Coloured families had incomes stated to be from R30 to R200 per month and these constituted the majority (Blacks 71,5 percent, Coloured 67 percent). Overall the admitted level of income in the Coloured group was higher with more families earning over R200 per month (16,9 percent vs 4,8 percent of Black families). Significantly more Black families (23,7 percent) had a negligible income below R30 per month than the Coloured group (16 percent) (X^2 test $p < 0,001$).

4.3.6. Family size and sibling deaths

Family size is shown in Figure 4.10. Most Coloured families (82,1 percent) had 1-3 children but fewer of the Black group (64 percent) fell in this category. Black infants came from larger families with 36 percent having 4 or more children. The incidence of deaths amongst siblings of the patients studied is reflected by Figure 4.11. There were significantly more sibling deaths in the Black Group (X^2 test $p < 0,0001$). As family size increased so did the incidence of sibling deaths (Figure 4.12). Multiple sibling deaths occurred in 7,5 percent of the families

Figure 4.10 FAMILY SIZE

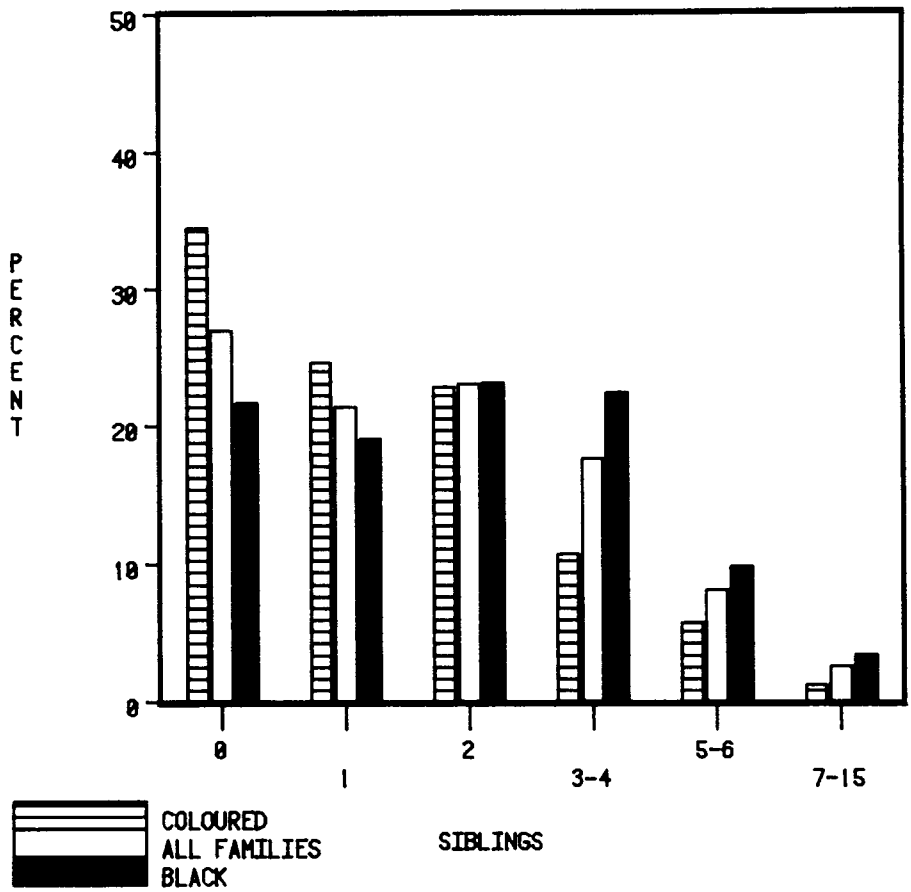


Figure 4.11 SIBLING DEATHS

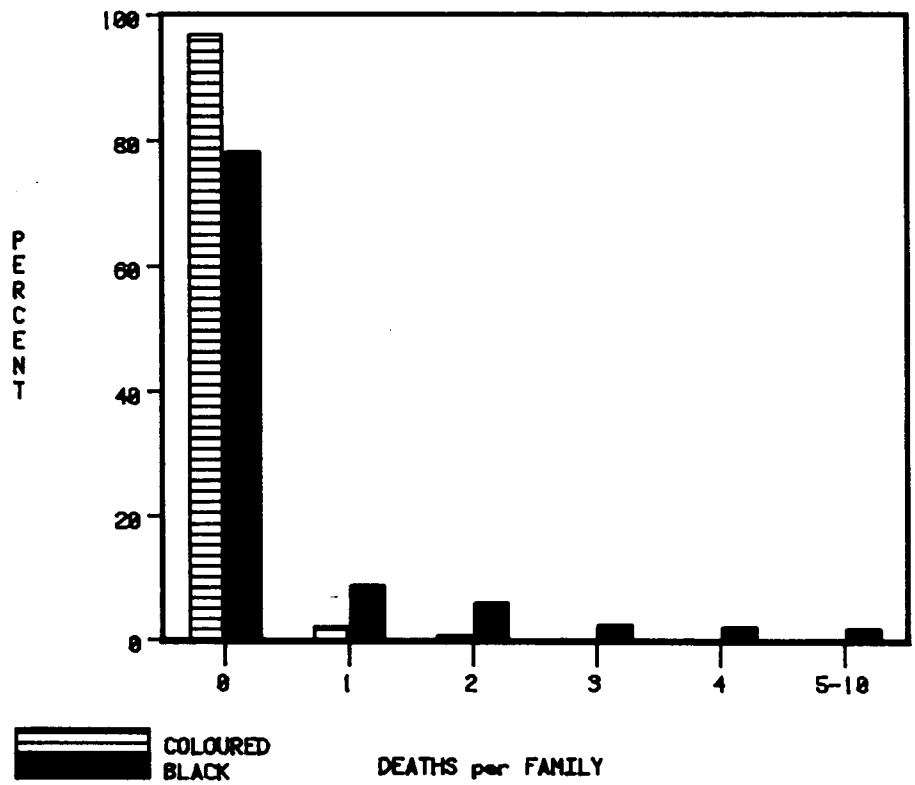


Figure 4.12 SIBLING MORTALITY vs FAMILY SIZE

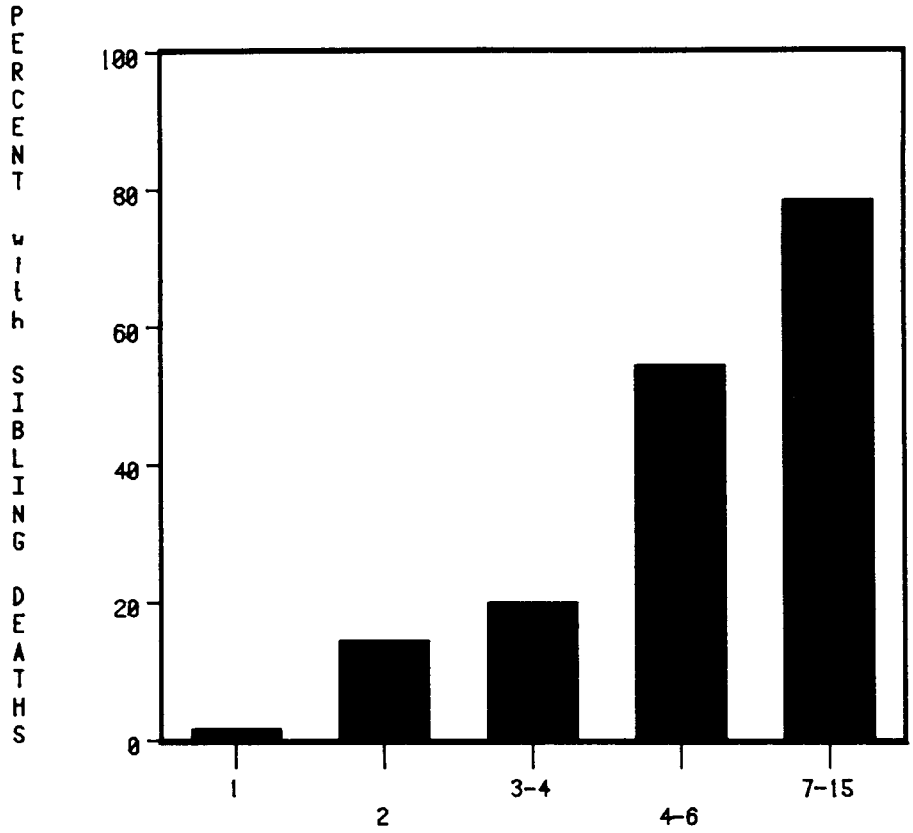
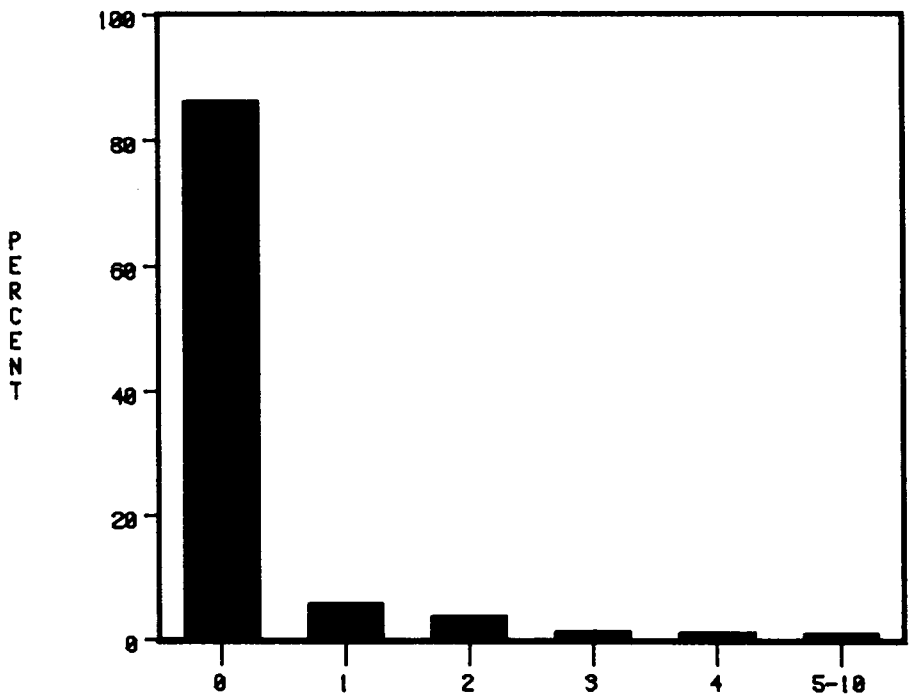


Figure 4.13 INCIDENCE OF SIBLING DEATHS



and most were in the Black group (Figure 4.13).

4.4 HOUSING

4.4.1. Location

Figure 4.14 shows areas, townships and districts from which the study group orginated. Black infants came predominantly from the Crossroad "squatter" area (50 percent) and the Guguletu township (24,7 percent) whereas Coloured families were more widely spread across the Cape Peninsula. A number of coloured infants (15,3 percent) were referred to the Children's Hospital from areas in the Western Cape outside the Cape Peninsula reflecting the significant Coloured population in these areas. The areas from which the patients studied originated are listed in Table 4.2.

4.4.2. Type of accommodation

Figure 4.15 summarises the type of accommodation occupied by the families at the time of admission of the infant to the rehydration ward. The "squatter" dwellings are designated shanties and in most cases are shelters of a "temporary" nature constructed with wood, corrugated iron and even plastic sheeting. There is no plumbing, sewage disposal or electricity provided. Water sources are communal taps at strategic points in the area. "Bachelor quarters" are hostels designed to accommodate unmarried migrant labourers and as such are

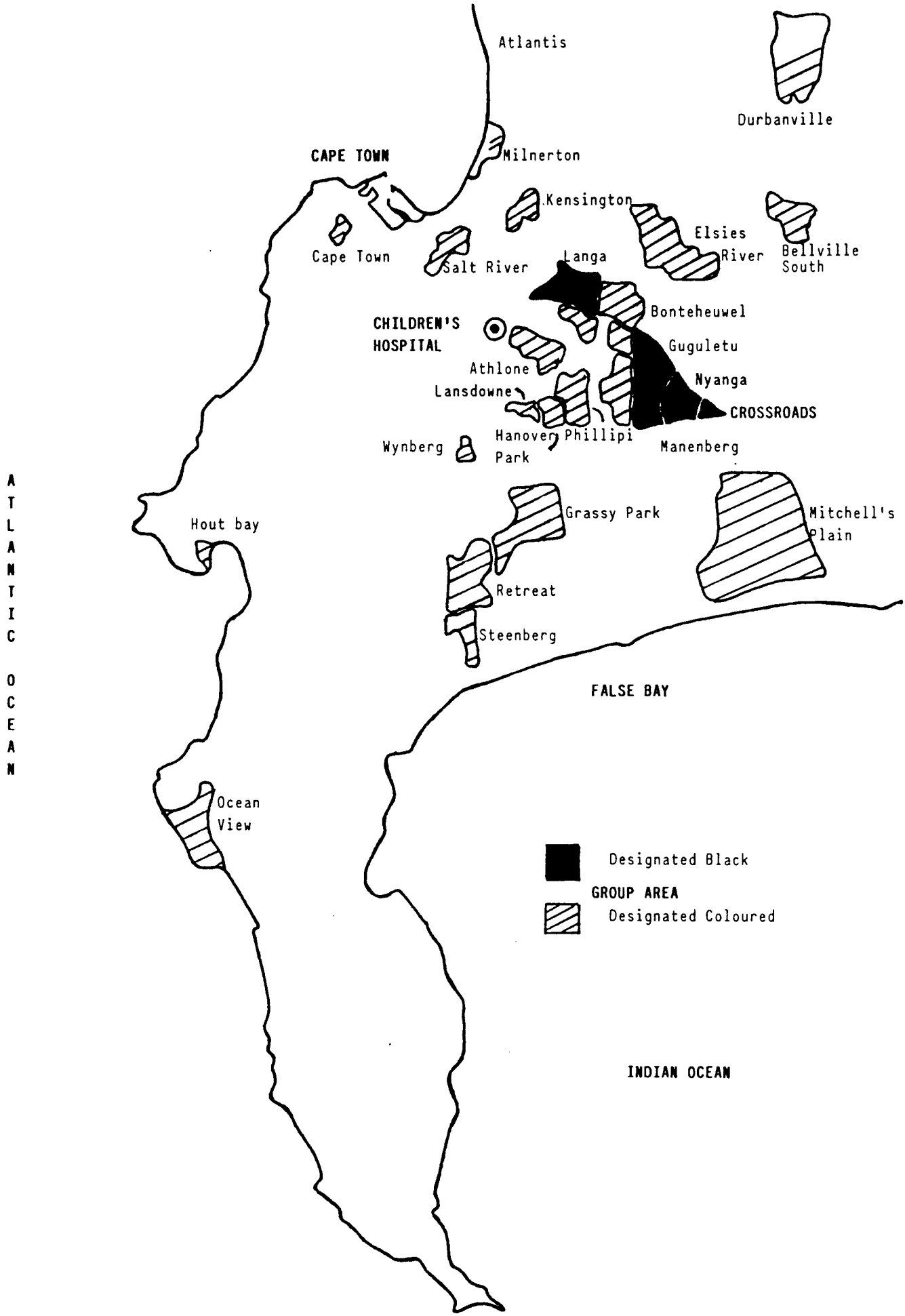


Figure 4.14 Map of Cape Peninsula

TABLE 4.2

ADDRESSES OF THE STUDY FAMILIES

BLACKS:

AREA	NUMBER	% TOTAL
[2] Crossroads	158	29,2
*+ Guguletu	78	14,4
+ Langa	58	10,7
+ Nyanga	21	3,9
[W] Constantia	1	0,2

COLOUREDS:

AREA	SOCIOECONOMIC GROUP	HOUSING TYPE	NUMBER
Athlone	IIa	1 *	8
Atlantis	IIa	*	3
Belhar	I	1	2
Bellville South	IIa	1	3
Bishop Lavis	IIb		9
Blackheath	IIa	*	1
Bonteheuwel	IIb	+ *	21
Bridgetown	IIa	*	1
[W]Constantia		1	1
Crawford	I	1	1
Eersteriver (Strand)			2

TABLE 4.2 (continued)

Elsies River	III IIb	2 +	16
Faure			1
^{W}Fishoek			1
Grassy Park		+ *	5
Hanover Park	IIb	+	7
Heideveld	IIb	+ *	2
Hout Bay	IIb	+	2
Kalsteenfontein	III	2	5
Kensington	IIa	1 +*	2
Lansdowne	IIa	1	4
Lavender Hill	IIb	+	2
Lentegeur			1
Lotus River	III		2
Macassar			2
Manenberg	IIb	+	13
Matroosfontein	IIa	1	2
^{W}Milnerton			1
Mitchell's Plain	IIa I	1	22
Ocean View		+	3
Ottery		2	1
Phillipi		2	16
Ravensmead	III		6
Retreat		1 +	6
Rylands Estate	I	1	3
Schotsekloof			1
Surrey Estate			1

TABLE 4.2 (continued)

Valhalla Park			2
Vanguard	IIa	1	1
Varkensvlei		2	1
Vrygrond (Steenberg)	III	2	6
Wynberg	I	1	1
Other Cape			35

SOCIO ECONOMIC GROUP[103]

I Highest socioeconomic group

II Middle socioeconomic group

(a) semiskilled workers

(b) unskilled workers

III Lowest socioeconomic group

often unemployed/unskilled

HOUSING TYPE[103]

+	Rented subeconomic housing	1	Owner occupied housing
*	Rented economic housing	2	Squatter/Slum area
W	Exclusively White suburb		

inadequately equipped as family dwellings. Shared accommodation refers in most instances to a rented room or in many, a room in a parent's or relative's home. If the family lived alone in a housing unit, either a flat or a house, they were regarded as having their own accommodation. A minority of Coloureds owned their own homes (mainly those living in Mitchell's Plain, Rylands Estate and in scattered instances elsewhere). Most lived in rented accommodation often subsidised (subeconomic) to a considerable extent by the Cape Town City Council (Table 4.2). The overwhelming majority of Blacks lived either in a shanty (50,2 percent) or in less than optimal hostel accommodation (27,1 percent). In contrast Coloured families were residing in either shared accommodation (63,5 percent) or in their own accommodation (29,6 percent).

4.5. FAMILY ORIGIN

4.5.1. Area

The origin of a particular family was taken as the area or district in which they had spent the longer period of residence. This information was available for 538 families (98.7 percent). Local residents orginating from Cape Town and its environs accounted for 221 families (41 percent). Most of these were coloured (179) with only a small number of Blacks indigenous to the Cape Peninsula. The remainder of Coloured families (50) came from areas in the Western Cape (the majority) or elsewhere in the Cape Province. Black families originated from Transkei (232) and Ciskei (31) and were thus "foreign" to Cape Town.

Figure 4.15 HOUSING

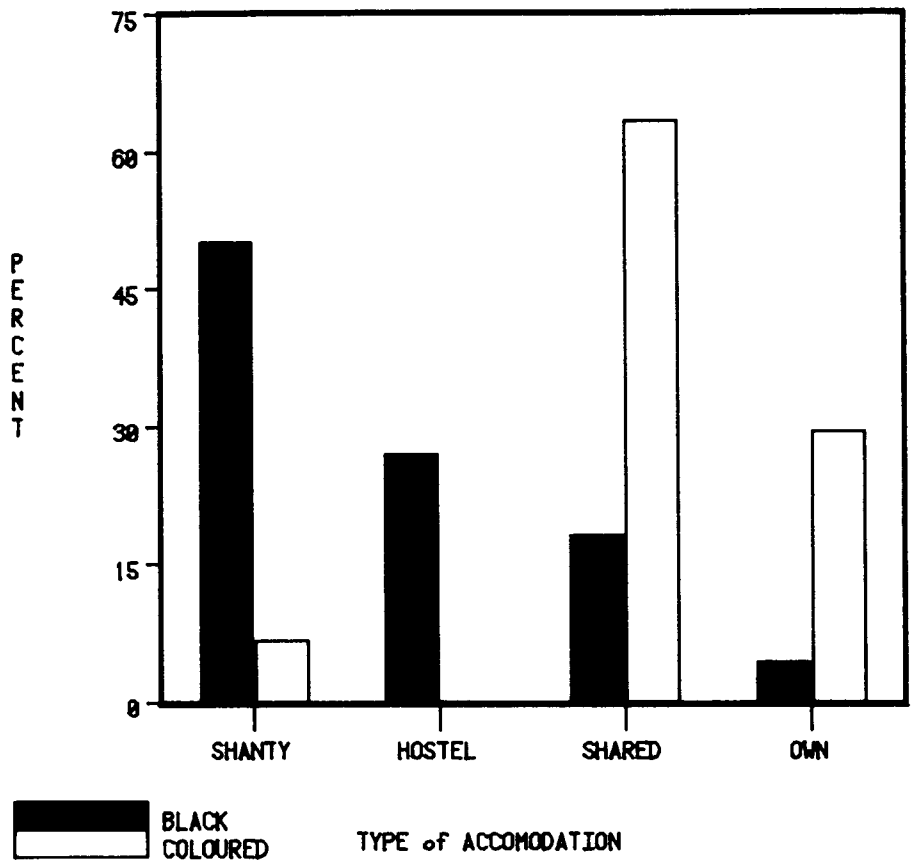


Figure 4.16 ORIGIN OF PATIENT FAMILIES

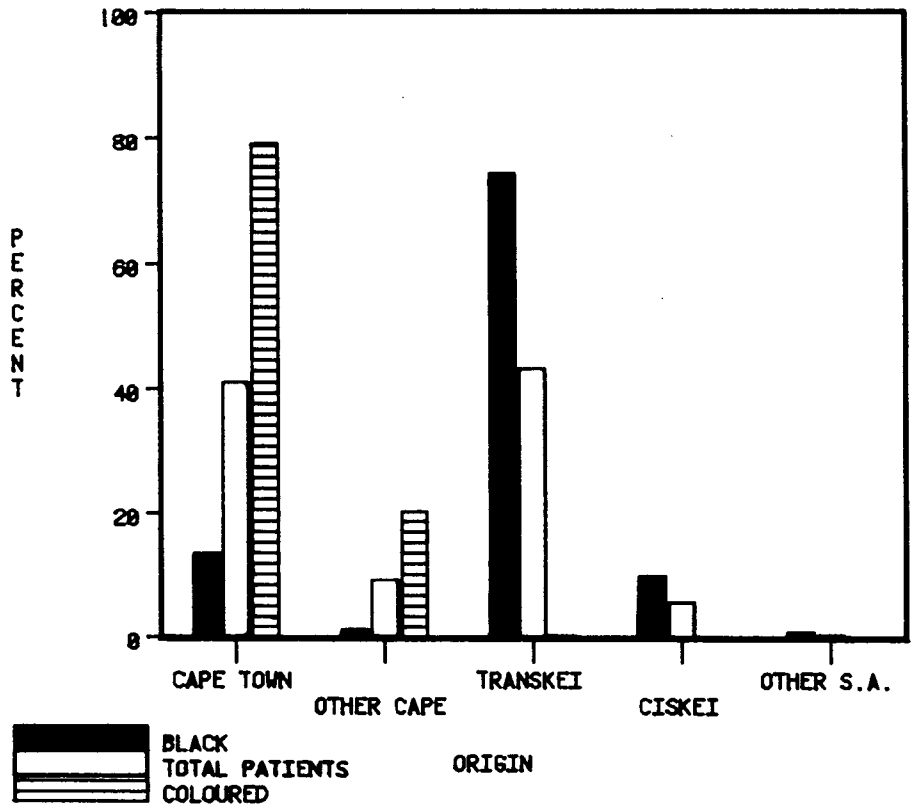


Figure 4.17 TIME SINCE ARRIVAL IN CAPE TOWN (excluding locals)

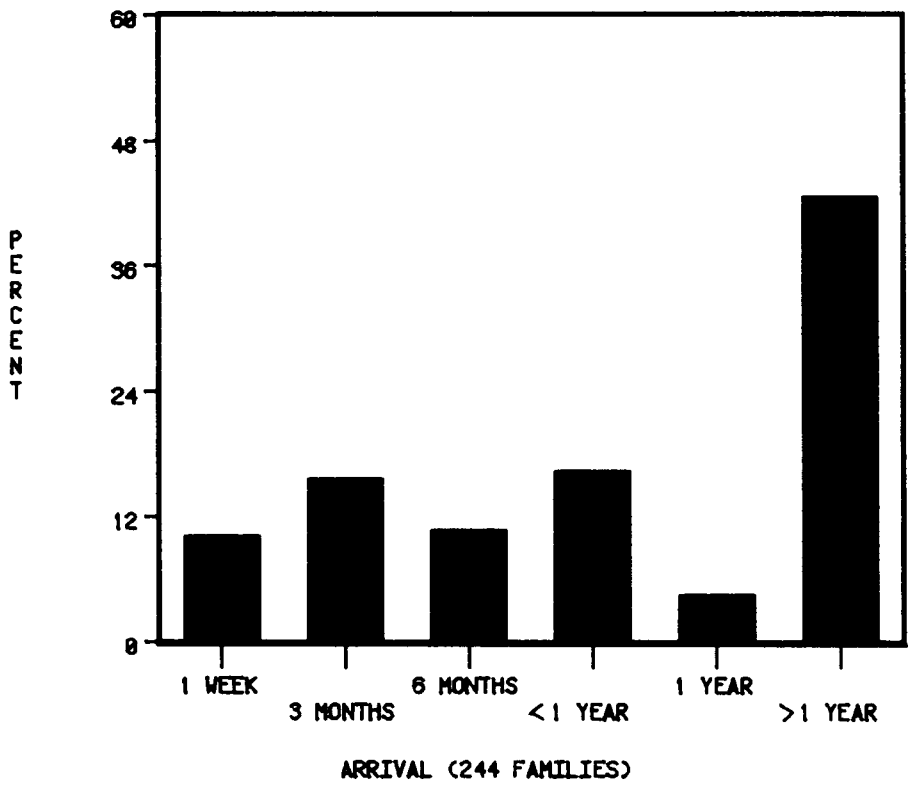


Figure 4.16 summarises the orgins of all the families of infants in the patient group.

4.5.2. Arrival in Cape Town

Local residents accounted for 255 families (46,8 percent) and the length of stay in Cape Town in this group was not relevant. In the remainder, the length of stay was known in 244 and the distribution is shown by Figure 4.17. With few exceptions these families were Black and 42,6 percent had been in Cape Town for more than a year before their infant was admitted to the rehydration ward. These infants had spent the period since birth in Cape Town. Some (10,2 percent) were admitted within a week of arrival while a further 15,6 percent had arrived in Cape Town 3 months prior to admission.

DISCUSSION:

The focus of this study was infants living in an urban or peri-urban environment. Despite the limitations of its hospital-based nature, the study provides useful information regarding the demographic, social, economic and to a lesser extent cultural variables in the population studied.

The Black or negroid group are mainly of the Xhosa tribe having their origins in Transkei and to a lesser extent Ciskei (Figure 4.1). Both these areas are independent "Black national states" within the Republic of South Africa, with a certain degree of autonomy from the central

government. As a group the Blacks are mostly rural and tribal in orientation but due to economic pressures there is considerable migration to urban areas such as Cape Town. Many then reside in urban or peri-urban squatter (shanty) areas in poor socioeconomic conditions without legal status or right to permanent residence.

The Cape Coloured, consequent to statutory controls imposed since the mid-1950's (Group Areas Act (No 41 of 1950) as enacted by the South African Parliament), reside in specific areas. Since the implementation of this Act the coloured population has been regarded as a totally separate society although according to the Theron Commission Report (1976) they share the aspirations and norms of White (caucasian) South African society[103]. Most (75 percent) are urbanised[143] although some are farm workers in the Western Cape. While Coloured housing is in many instances overcrowded and inadequate, it is generally permanent with a reticulated water supply, adequate sewage disposal and often electrified. The Coloureds have the right to permanent residence and benefit from a preferential employment system in the Western Cape.

All the infants studied had a common illness and in this sense are a single group. Nevertheless the two ethnic groups are distinct as outlined above. A discussion of the socioeconomic and demographic data relating to all groups is relevant. The majority (86,7 percent) of the infants were delivered with medical assistance (or presence) either in hospital or in the local clinic indicating the availability of medical services in the community (this refers mainly to the Cape Peninsula). Infants delivered at home were mostly Black and from Transkei where medical services are less accessible.

Birthweights were generally in the normal range but those below 2,5 kg were more often Coloured infants (24,6 percent). A high incidence of light for dates infants in the Coloured population has previously been reported from Cape Town[163]. Whether this places such infants at risk and indicates maternal malnutrition remains to be determined. A comparison with other reports (Table 4.3) shows 24,6 percent to be one of the highest recorded. A study of malnourished children in Jordan[3] showed that a low birthweight was significant ($p < 0,05$) for the occurrence of malnutrition. In the present study a birthweight of less than 2,5 kg was significantly associated with a rehydrated weight less than 80 percent expected for age (X^2 test $p < 0,0001$). It seems that these light for dates Coloured infants are at risk for later malnutrition and that this may be an important contributory factor to the development of diarrhoeal disease. The birthweights for Black infants (in this study) correspond to figures quoted for American Negroes[7,96] with 9.9 percent under 2,5 kg in Cape Town compared to 11,2-13,8 percent for the American Negro infants.

Infant feeding practices showed no relation to the place of birth (i.e. hospital or home) which is similar to the findings of Manderson[92] in her study of Malaysian infants and French in her study of Navajo infants[49]. This is contrary to the view that separation of the infant from the mother in hospital and the hospital environment mitigate against the initiation of breast feeding as expressed by several authors[72,97]. The incidence of breast feeding was low (30 percent) and only 2 infants were exclusively breast fed at the time of admission (0,4 percent). This is in agreement with the widely accepted view that diarrhoeal disease occurs frequently after weaning and is associated with a low frequency of breast feeding[53,73,75,135]. In addition the

TABLE 4.3

INFANTS OF LOW BIRTHWEIGHT[1] (LESS THAN 2,5 kgm)

Netherlands	3,5%
+Alaska (Eskimo)	6,8%
New Zealand	5,6%
U.S.A. (White)	7,2%
+U.S.A. (White California)	5,8%
Bantu (Black, South Africa)	11,6%
*Black (Cape Town 1981/82)	9,9%
U.S.A. (non-white)	13,8%
*Coloured (Cape Town 1981/82)	24,6%
Indian (South Africa)	18,3%
Indian (Calcutta)	34%

* Incidence obtained by the current study

1 Table from RE Behrman. The Fetus and the Newborn. Chapter 7. In: Nelson Textbook of Pediatrics 10th Ed. V.C. Vaughan RJ McKay eds. WB Sanders, Philadelphia 1975 : 342.

\+ JE Maynard LM Hammes. A study of Growth Morbidity and Mortality among Eskimo Infants of Western Alaska. Bull Wld Hlth Org 1970 : 42,616.

duration of breast feeding was extremely short in the majority of infants as only 48 percent were breast fed beyond 3 months and 18 percent beyond 6 months of age. In a study of Ethiopian infants under the age of 2 years with acute diarrhoea Thoren et al[149] found that 47 percent were not breast fed but a similar incidence was found in their control group (43 percent). More controls were breast fed up to six months of age (36 percent) than the patients (8 percent) and this appeared to be the significant difference. Breast feeding was especially infrequent amongst the Coloured infants with only 19 percent partially breast fed at admission. In a study of 120 Coloured children without diarrhoea Wittman et al[160] found that 82,5 percent had been weaned by 6 months of age and at the end of the first year this had risen to 97,5 percent. This was despite the higher degree of education noted in the Coloured mothers. Cunningham[34] in a rural American setting found breast feeding was associated with a higher level of parental education and by inference socioeconomic status. The reverse was shown by Plank and Milanesi[111] where in rural Chile improved living standards accelerated weaning and infant mortality rose with income.

Amongst the Black infants in the current study 39 percent were still partially breast fed on admission. Freiman et al[48] in their study of Black infants with gastroenteritis found only 1 percent to be solely breast fed and 25 percent partially breast fed. In a study of 717 infants aged up to 36 months (63 percent under 1 year) with and without diarrhoea (almost equally distributed) Spencer and Coster[142] report 10 percent wholly breast fed and a further 39 percent partially breast fed. Their study had a wider age range including infants under 6 weeks of age and the incidence of breast feeding was thus higher than in this study.

The protective role of breast feeding against gastrointestinal, respiratory and allergic disorders seems well established[33,34]. This appears to be more evident in the developing areas of the world amongst the lower socioeconomic segments of the population[72,73] but is also true in developed countries[33,84]. Breast milk contains secretory IgA (there is no endogenous source of mucosal secretory IgA in the newborn), Lyzozyme and lactoferrin all with anti-infective properties. In addition there are macrophages, T and B lymphocytes necessary for an adequate immune response present in breast milk[33]. This protection is needed for the first 3-4 months whilst the secretion of endogenous mucosal secretory IgA increases to adequate levels. It has been reported that IgA is active against rotavirus and that breast fed infants have fewer infections and less intense colonisation by rotavirus[33]. It has been shown that a specific strain of E.coli ingested by a pregnant woman will stimulate the production of a specific IgA antibody against that strain, stimulation presumably acting via the gut-associated lymphoid tissue (GALT)[51]. On the other hand Schoub et al failed to demonstrate specific antirotavirus immune factors in human breast milk[134]. They suggest that the association of bottle feeding with diarrhoea is due to an increased opportunity for infection.

That more Coloured infants had been weaned at the time of admission probably reflects the higher degree of urbanisation amongst this community. It may be that Black infants develop diarrhoea despite being more frequently breast fed as a result of heavy environmental contamination (i.e. water, foodstuffs and physical environment) which overwhelms a normally adequate host resistance. The Coloured group with a greater loss of the protective effects of breast feeding may be more susceptible to a lower pathogen load.

The parents not unexpectedly tended to be young with the median maternal age 24 years and the mean 25,5 years. Figure 4.7A and 4.7B show the Coloured parents to be younger than their Black counterparts. This difference is significant ($p < 0,01$). A comparison of the age range of all coloured mothers having live births in South Africa[143] for 1980 with the Coloured mothers of the study infants shows a similar pattern. This group was not significantly younger than the average (Table 4.4). Corresponding statistics were not available for black women.

The level of maternal education was deemed relevant as most of the infants were in the full time care of their mothers. The level of education or literacy could be a significant limiting factor in any health promotion scheme aimed at this group. Twenty six percent of the mothers had either received no education (illiterate) or had attended school for three years or less (semi literate) and were probably unable to competently follow written instructions. A further 44 percent had received primary education while 30 percent had received secondary education (literate). Overall the Black mothers were less educated (Figure 4.7B), although the numbers achieving the secondary level did not differ significantly (Figure 4.7A). Literacy rates were higher than the average for both Black and Coloured mothers if compared with figures obtained from the 1980 National Census[143]. The average rate in Blacks was 51 percent and in the Coloured population 69,7 percent. Wittman et al[160] in their study of Coloured mothers in the Cape Peninsula (1964) found 6 percent to have received no effective education, while 24 percent had been educated to Standard 1-3. A further 36,2 percent had reached Standards 4 or 5 and 33,6 percent had been educated beyond this level.

TABLE 4.4

COLOURED MOTHERS : AVERAGE vs STUDY GROUP AGES

	< 20	20-24	25-29	30-34	35-39	40-44	> 45
	YEARS						
	%	%	%	%	%	%	%
Average[143]	16,8	33,9	25,1	14,5	6,6	2,5	0,5
Study Group	19,9	38,5	24	10,5	3,6	2,3	0,9

A large number of the parents were unmarried (50,7 percent). This trend was more marked amongst the Coloured mothers (56,4 percent). Fewer Black parents were unmarried (44,1 percent) reflecting possibly persisting adherance to traditional customs. The number of unmarried Black mothers is nevertheless high when compared with traditional Black tribal communities where most are married according to local custom. The large number of unmarried Black parents reflects the degree of social disruption associated with migration to periurban slum areas.

A high percentage of the families studied had one parent in full-time employ (Coloured families 84 percent, Black families 77 percent) with an overall figure of 80,5 percent. Most mothers were full time housewives with only 5,5 percent working. Many especially amongst the coloured group had worked previously but had stopped work after the birth of their children. It is presumed that many would return to work in due course as the infant required less attention. Many indicated that this would be the case. Very few of the Black mothers indicated their intention to work outside the home in the future. In an evaluation of children in the age group from birth to 3 years, Wittman et al[160] found that 44,2 percent of Coloured mothers were employed. Those women in the lower income group were mostly domestic or factory workers, while the higher income group were more often employed as factory or clerical workers. It appeared that most Black fathers were employed as semiskilled or unskilled manual labourers largely on a contract basis. This information was not entirely reliable as many of the Black mothers were unsure of the nature of the father's work.

Closely allied to employment was the income of the family. Spencer and Coster[142] comment in their paper on the epidemiology of gastroenteri-

tis in infancy in Johannesburg that uncorroborated estimates of the income from a history are unreliable. Black mothers, grandmothers or older children accompanying the infants often have no concept of the breadwinner's earnings nor have the traditional status to convey such information. Tribal black women have a subservient role in their society. They are not free to act without the husband's permission and are reluctant to disclose the family income in his absence. Wittmann et al[160] cite further reasons for inaccurate assessment of family income. Employment is often temporary and wages thus vary. In addition as rent is determined on the family income this may result in a reluctance to divulge the correct amount or lead to an underestimation. Hospital fees are also scaled to family income mitigating against an accurate estimation of income. All the factors outlined would tend to produce a range of income lower than the actual figure. In this study those with no idea of the breadwinner's income (12,7 percent) were mostly Black. The average monthly income for the Coloured population in 1981 was reported at R310 while for Blacks the corresponding estimate was R228[113,143]. The Household Subsistence Level (H.S.L.) in Cape Town for 1982 was estimated by the Institute of Planning Research, University of Port Elizabeth to be R260 for a Coloured family of 5 persons and R257 for a Black family of 6 persons[113]. The income levels (Figure 4.9) are subject to the reservations outlined and are probably an underestimation of the true family income. The mean monthly income acknowledged in the Coloured families was R130 per month while the figure was R82 for the Black families. It is clear that despite the slightly smaller family size than the standard (Figure 4.10), the majority had an income of below the H.S.L. The Afrikaanse Handelsinstituut estimated the average income of Coloureds in the non agricultural sector (excluding the professional group, for example

lawyers, medical practitioners etc) during 1981 at R309 monthly and a corresponding income for the Black group R228 per month. Incomes in various sectors of the work force for 1981 are reflected in Table 4.5. If these estimates are accepted the family income of the study group falls well below the average and identifies these infants as originating from a severely economically depressed section of the community. Poverty may be assumed to be a factor placing these children at risk.

The families were generally small with 71,5 percent having 3 or fewer children which is similar to the findings of Manderson[92], in her study. This may be explained by the youth of the parents. Coloured families tended to be smaller with 82,1 percent having 3 or fewer children as opposed to 64 percent in the Black group. An increase in the family size was paralleled by an increase in the number of families in which one or more siblings had died (Figure 4.12). In the larger families multiple sibling deaths were not infrequent. The majority of sibling deaths occurred amongst the black families (7 sibling deaths in the Coloured group versus 68 sibling deaths in the Black families) which is a significant difference (X^2 test $p < 0.0001$). Many of these infants had died of either diarrhoeal disease or other infectious diseases.

For the majority of both ethnic groups, environmental conditions were less than optimal (Figure 4.15). The Black infants generally were more poorly housed than Coloured infants with 50 percent residing in slum conditions. Coloured housing although more permanent was often overcrowded with 63,5 percent in shared accommodation. These families occupied a single room. This picture is mirrored by most other studies from the developing world[108]. Diarrhoeal disease is a particular problem of the sprawling periurban slums surrounding many cities and

TABLE 4.5

[1]AVERAGE MONTHLY EARNINGS IN VARIOUS SECTORS OF SOUTH AFRICA

	COLOURED PEOPLE	BLACK PEOPLE
	R	R
Total	293	216
Mining	361	201
Manufacturing	297	255
Electricity	425	256
Construction	328	193
Trade and Accommodation Services	231	165
Transport and Communications	246	242
Finance and Insurance	417	305
Government and Services	307	208

[1] National Manpower Commission Report[113]

towns in these areas[72,97]. Spencer and Coster[148] in their study in Johannesburg amongst a mainly Black population found subtenancy a common occurrence. Although not permitted by the authorities 30 percent of the households consisted of 10 to 14 members. Subtenancy was particularly common among the Coloured families studied. A consideration of the living conditions of the families shows two distinct populations split along ethnic lines. Firstly the Black predominantly migrant group that arrived in Cape Town at intervals ranging from less than a week to over a year previously. This Black migrant group residing in the Crossroads "squatter" area was identified in this study as the source of the largest group of patients. Only a minority of the Blacks studied could be termed indigenous to the Western Cape. Secondly the Coloured group that is indigenous to the Cape Peninsula as outlined above and who are mostly permanent residents of the Cape Peninsula. Preventitive measures and intervention in the squatter areas could have a major effect on the number of admissions annually to the rehydration ward.

CONCLUSIONS

What conclusions can be drawn from a synthesis of the socioeconomic and demographic data presented in this chapter? The place of birth had no predictive value. The high incidence of low birth weight babies in the Coloured group was identified as a probable risk factor. The young often unmarried parents generally had 1-3 children and a lower than average income living in inadequate overcrowded conditions. Most mothers were at home and presumably looking after the infant but many had been weaned especially if over 6 months of age. There were substantial differences between the two ethnic groups. The Coloured parents were younger, less often married and had smaller families. In many instances the family

shared accommodation with grandparents. The incidence of breast feeding was extremely low amongst Coloured mothers who generally had a higher level of education.

Black parents tended to be older, more often married and had larger families. The incidence of breast feeding was low but significanly higher than the Coloured group. Other characteristics of the Black families were the often squalid environment, the higher incidence of the death of a sibling (frequently from diarrhoeal disease) and the largely migrant population from which they came.

It seems reasonable to conclude that the Coloured group constitutes a sample from a subgroup at risk in the Coloured population. This subgroup forms part of the lower socioeconomic strata of the community and these infants may be more susceptible to the pathogenic mechanisms operative in their environment as a result of the factors already discussed. In contrast the Blacks are probably representative of a wider spectrum of the Black community which overall is much poorer and has a less than optimal environment. The Black infants may inherently be less at risk (i.e. more often breastfed, higher birthweight and in a better "mothering" situation as a result of an older more experienced mother) but are overwhelmed by the massive load of pathogenic agents in the contaminated environment. The Black group coming predominantly from one area is easier to identify and more likely to benefit from direct intervention such as improved housing, a secure water supply and adequate sewage disposal. It is of interest that while a contaminated food and water source is often incriminated it appears that the pathogenesis is more complex than direct infection in the majority of cases. Bokkenheuser and Richardson[17] in a study on rural Bantu school

children found salmonellosis to be a common occurrence, but the wells (water source) although contaminated with faecal E.coli contained no salmonella or shigella.

Home based oral rehydration therapy has been acepted world wide as a major factor in reducing mortality and morbidity in infantile diarrhoea[18,63,105,108,127] (Chapter 1). This study suggests that such a program for the Black community may be highly cost effective in significantly reducing rehydration ward admisisons as 43,6 percent of the total studied originated from the two Black areas of Crossroads and Guguletu. Specific intervention directed at the coloured group could be more difficult as the cases were more widespread and formed a small subgroup of the total population.

This study does not allow an estimation of the overall incidence of diarrhoeal disease in the Black and Coloured populations of the Cape Peninsula but the incidence appears lower in the Coloured group. This is suggested by the lower admission rate to the rehydration ward from a larger local population (773060 Coloureds versus 188160 Blacks in the urban areas of greater Cape Town[143]).

In conclusion an hypothesis could be advanced that in the Coloured group the problem is predominantly inadequacy of the parents with an inability to cope with the pressures of urban society and a resultant lack of competent parenting. In the Black group the major factor is the overwhelmingly inadequate environment which negates the fact that most may be inherently competent parents. There is little doubt that in both groups the situation is exacerbated by financial pressures. While the solution to this problem is complex it can be expected that any

intervention that improves the general standard of living will have a most dramatic effect in reducing the incidence of diarrhoeal disease amongst the black infant population. As a short term measure the initiation of a home-based oral rehydration program directed at the Blacks concentrated in the Crossroads area and other townships would seem urgently needed and likely to be highly cost effective. While amongst the lower socioeconomic strata of the Coloured population promotion of breast feeding for young infants and health education is a priority.

CHAPTER 5

CLINICAL DATA

On admission to the rehydration ward a history was taken from the escort of the infant whom in most cases was the mother. Findings on physical examination together with the results of all investigations undertaken are presented with the exception of stool cultures (see Chapter 6). The course in the rehydration ward, outcome and the subsequent progress are also recorded. In many cases the patient was seen at home after discharge by a health visitor as part of the routine follow up of these children. A report from this health visitor when available was an additional source of information on their subsequent course.

A history was not taken from the escorts of the control subjects other than to exclude the presence of diarrhoea at the time and in the preceding month. They were not examined and only the age, race, sex and bodyweight were recorded. These parameters are compared with those for the patient group. The standard fluid therapy regime used in the rehydration ward is included in Annexure D.

RESULTS:

5.1. HISTORY

5.1.1. Diarrhoea

An adequate history of the duration of the diarrhoea was available in 540 patients. In 256 (47,4 percent) the diarrhoea had been present for less than 2 days, in 111 (20,6

percent) there was a history of diarrhoea for 2 to 3 days and in a further 69 patients (12,7 percent) 3 to 4 days. Thus 80 percent of the patient group had a history of diarrhoea for 4 days or less prior to admission to the rehydration ward. Diarrhoea had progressively worsened in 456 patients (84,4 percent) and in the rest it was either intermittent or of unvarying severity from the onset.

5.1.2. Vomiting

There was no vomiting in 23 percent of patients. Vomiting for 1 or 2 days prior to admission occurred in 281 patients (52,1 percent) and a further 68 patients (12,6 percent) had vomited feeds for 3 days. A history of vomiting for more than 3 days was unusual (13 percent) and in these it tended to be intermittent episodes. In the majority (97,5 percent) the onset of vomiting coincided with the onset of diarrhoea. Vomiting was the presenting symptom in only 2,5 percent.

5.1.3. Other Symptoms

No associated symptoms were reported in 116 patients (21,3 percent). A cough either alone (22,4 percent) or associated with fever (34 percent) was the commonest associated symptom. Fever alone was reported in 110 patients (20,2 percent). In most cases the temperature had not been measured at home and fever was accepted as having been present if the mother (or other escort) considered the infant to have felt hot.

Six children had convulsions associated with the diarrhoeal episode prior to admission. In 5, the mother felt that the infant had been febrile at the time of the convulsion and all were described as generalised in character. No other symptoms were recorded although the overwhelming majority of the mothers reported that their infants had been non- specifically irritable from the onset of the diarrhoea.

5.1.4. Treatment for the Diarrhoea prior to Admission

Oral rehydration solutions were generally not given in the home at the onset of diarrhoea. Two hundred and sixty six patients (40 percent) had not been seen during the course of the presenting diarrhoeal episode by a doctor, clinic, nurse or traditional healer (witchdoctor or herbalist). A general practitioner (in private practice) had been consulted in 14 percent, 19,6 percent had been treated at either a local "day hospital" or clinic and some infants (12,3 percent) had been treated in the outptient's department of the Red Cross Children's Hospital prior to admission. Only six patients (1,1 percent), all Black had been taken to a traditional healer during the course of the presenting illness.

5.1.5. Previous Admissions to Hospital

The majority (75 percent) had never been admitted to the rehydation ward previously. In 83 infants (15,2 percent) there was a history of prior admissions to the rehydation ward and of these 44 had been admitted less than 1 month previously.

Admissions to the Red Cross Children's Hospital for conditions other than diarrhoea were infrequent (5,1 percent) as were admissions to other hospitals (4,2 percent). Multiple previous admissions to hospital for either diarrhoeal disease or other conditions were unusual and occurred in only 9 cases (1,7 percent).

5.2. PHYSICAL EXAMINATION

5.2.1. Age

The age range for the patient and control group is shown in Figure 5.1. In both groups there was a predominance of infants aged 3 to 6 months and this was more marked in the control group. The difference was not statistically significant.

5.2.2. Race

There was 316 Black infants (58 percent) and 229 Coloured infants in the patient group (42 percent). The Control group consisted of 96 Black infants (32,3 percent) and 201 Coloured infants (67,7 percent).

5.2.3. Sex

There were 276 males and 296 females in the patient (ratio 1:1,1) compared with 162 males and 135 females in the control group (ratio 1,25:1).

Figure 5.1 AGE RANGE

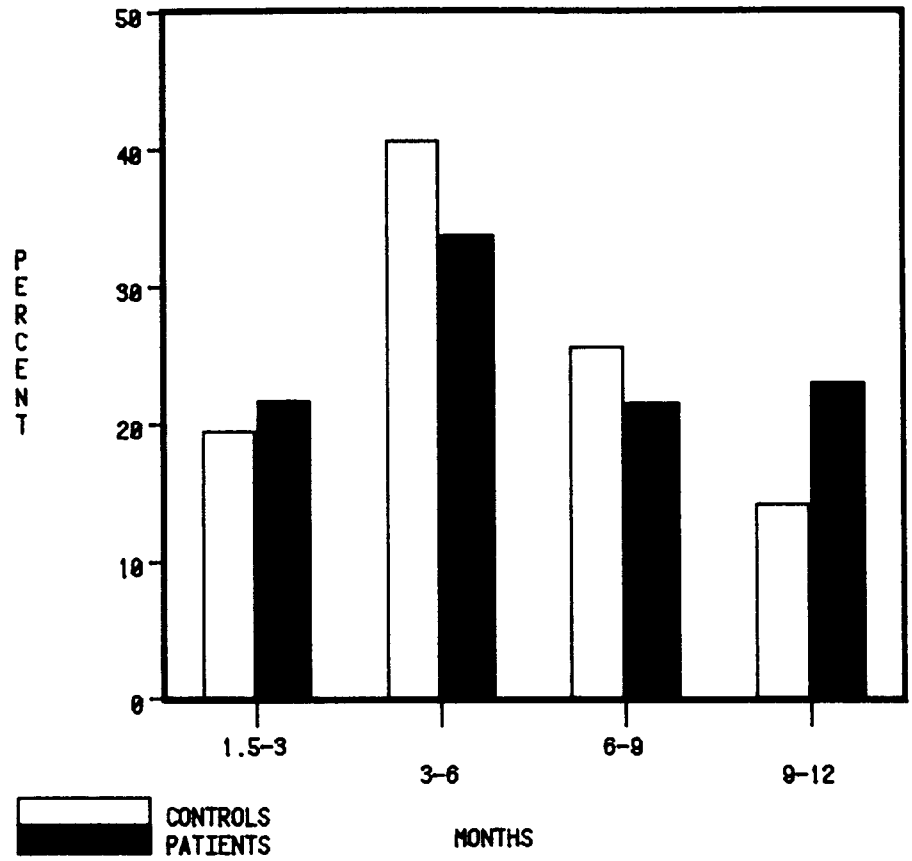
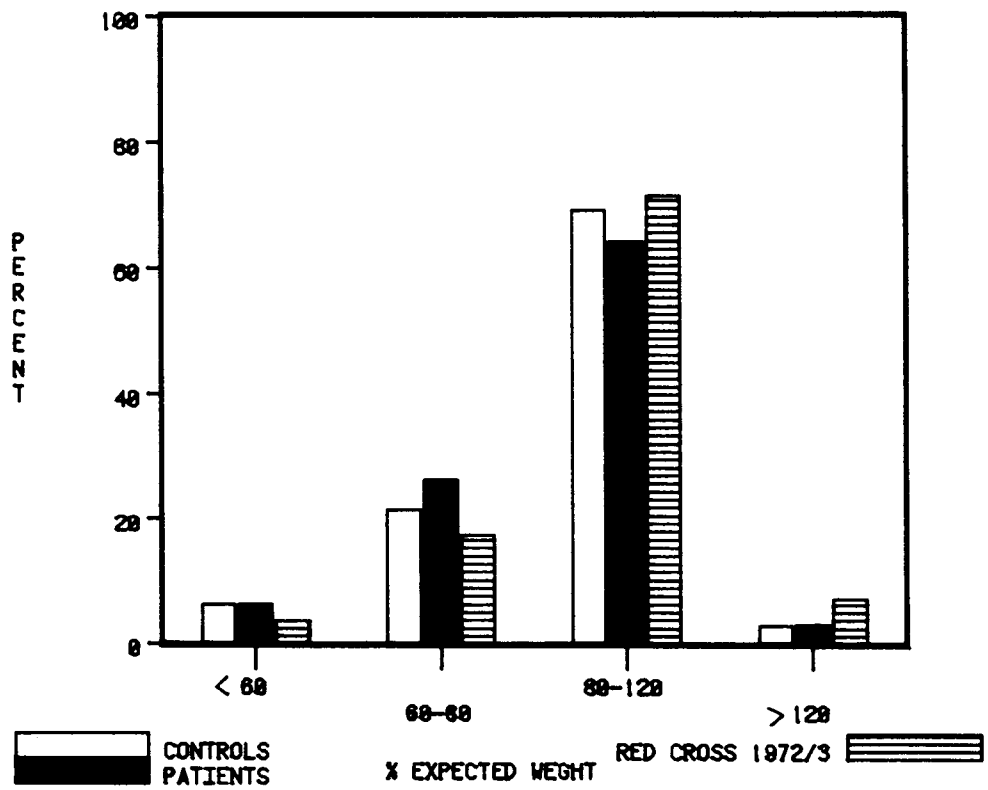


Figure 5.2 NUTRITIONAL STATUS



5.2.4. Bodyweight

The admission and discharge weights were recorded for all 545 patients. A single body weight was recorded for each control infant. To enable comparison the weights are expressed as a percent of expected weight for age. In the patient group 6,4 percent were below 60 percent of expected weight (marasmic), 26 percent between 60 and 80 percent of expected weight (under weight) and 67,6 percent above 80 percent of expected weight for age (normal). The control group showed a similar distribution of body weight with 6,4 percent below 60 percent, 21,4 percent between 60 and 80 percent and 72,2 percent above 80 percent of that expected for age. Statistically there was no difference between the patient and control groups. The results are shown in Figure 5.2. Also included in the figure are previous values obtained from a survey of children under on year of age attending the Children's Hospital outpatients during 1972 - 1973[158]. This data allows comparison with a sample of infants of similar age seen in the outpatients department of the Children's Hospital.

There is no statistically significant difference between the patient and control groups with regard to bodyweight. In the patients comparison of Black and Coloured infants shows that more Coloured infants were less than 60 percent (marasmic) and between 60 and 80 percent of expected weight (underweight). The difference is not statistically significant (X^2 test p values 0,07 and 0,06 respectively).

TABLE 5.1

DEGREE OF DEHYDRATION

DEHYDRATION %	ESTIMATED n = 545 Patients %	*CALCULATED n = 530 Patients %
0	4,8	13,4
Borderline	24,6	9,1
5	47,9	23,1
Intermediate > 5 < 10	10,1	39,7
10	8,8	12,8
⩾ 15	3,8	1,9
Total ⩾ 5% dehydrated	70,6%	Total ⩾ 5% dehydrated 77,5%

* Calculated percent rehydration = $\left(\frac{\text{Discharge weight - Admission weight}}{\text{Discharge weight}} \times 100\right)$

TABLE 5.2

COMPARISON OF CLINICAL ESTIMATION OF DEHYDRATION WITH THE CALCULATED VALUE

CALCULATED PERCENT DEHYDRATION	CLINICALLY ESTIMATED DEGREE OF DEHYDRATION TOTAL 530 PATIENTS				
	Normal/ Borderline n = 155	5 percent n=258	7,5 per cent n=55	10 percent n=41	15 per cent n=21
< 5	110	105	12	4	7
5	28	77	11	13	5
7,5	10	49	14	5	1
10	4	27	16	15	7
15	3	0	2	4	1

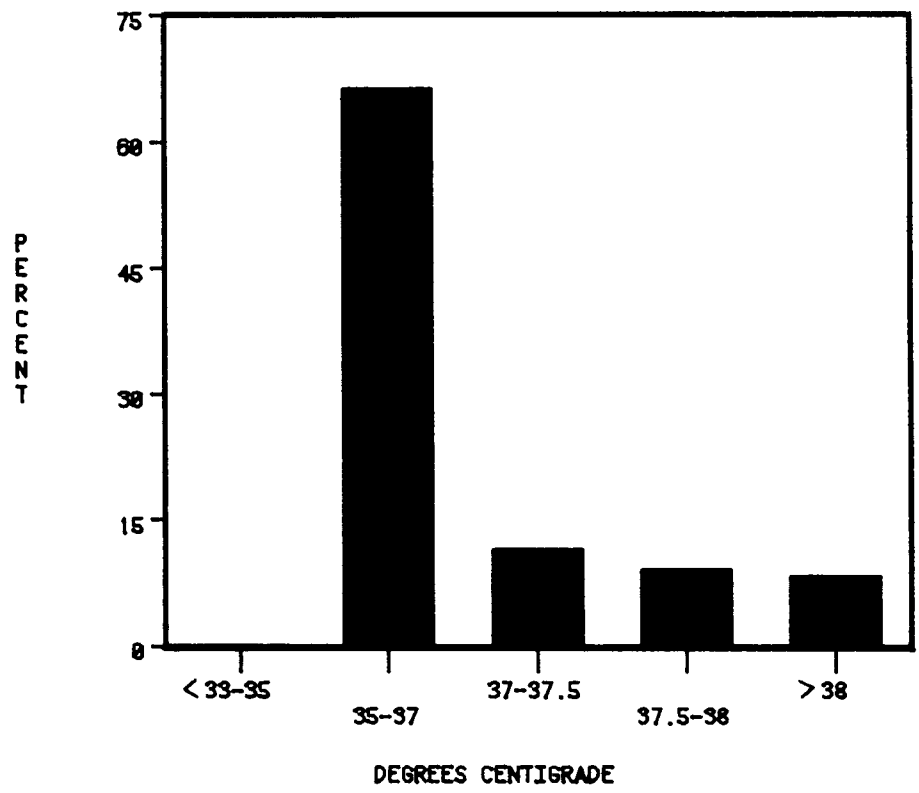
5.2.5. Dehydration

The range of dehydration found in the patient group is shown in Table 5.1. The clinical estimation of the degree of dehydration using parameters such as loss of skin turgor, sunken eyes, dry mouth and tongue and depression of the fontanelle is given. For the detailed criteria used in the clinical assessment of the degree of dehydration see Annexure E. Patients with evidence of shock as reflected by a disproportionate tachycardia, a prolonged capillary filling time (over 5 seconds) indicating poor peripheral perfusion and/or hypotension were regarded as more than 15 percent dehydrated. The actual degree of dehydration was calculated from the admission and rehydrated discharge weights. Due to persistent dehydration at the time of transfer from the rehydration ward this could not be calculated in 15 infants. A comparison of the clinically estimated and calculated degree of dehydration is given in Table 5.1 and 5.2. By clinical estimation 5 percent or greater dehydration was present in 70,6 percent of patients and from the calculated values 77,5 percent were dehydrated to this degree (Table 5.1). Overall the tendency was to clinically underestimate the degree of dehydration. This was particularly so in infants with dehydration ranging from borderline to less than 10 percent (Table 5.1). In 217 patients (41 percent) the estimated and calculated degree of dehydration were the same (Table 5.2).

5.2.6. Body Temperature

The axillary temperature was recorded for 520 infants on admission. The results are shown in Figure 5.3. The majority

Figure 5.3 BODY TEMPERATURE



(66,3 percent) had a body temperature within the normal range (35°C to $<$ 37°C). In 29,2 percent the axillary temperature was elevated above 37°C and in 8,4 percent it was elevated above 38°C. Hypothermia was uncommon with only one reading below 35°C.

5.2.7. Pulse Rate and Blood Pressure

The pulse rate was recorded in all the infants studied and the distribution of these values is reflected by Figure 5.4. Blood pressure (mm of mercury) was not recorded in 131 infants (24,1 percent) as when initially seen there was no clinical evidence of shock and they were small infants in whom the procedure was difficult and time consuming. In the remainder the systolic blood pressure measured in the arm at the brachial artery was recorded and the results are shown in Figure 5.5. A comparative tabulation of the pulse rate and systolic blood pressure in 413 infants is presented in Table 5.3. There was no clear relationship between pulse rate and blood pressure readings. The majority (71,4 percent) had a pulse rate between 130 and 160 beats per minute. Most infants (86,4 percent) had a systolic blood pressure in the range from 60 to 110 mm of mercury. Significant hypotension (blood pressure below 60 mm of mercury) occurred in 10,2 percent of the patients on admission.

5.2.8. Upper Respiratory Tract

An upper respiratory tract infection as evidenced by pharyngitis and coryza was present in 20,6 percent of the patients. Clinical evidence of oral candidiasis was present in 11,2 percent.

Figure 5.4 PULSE RATE

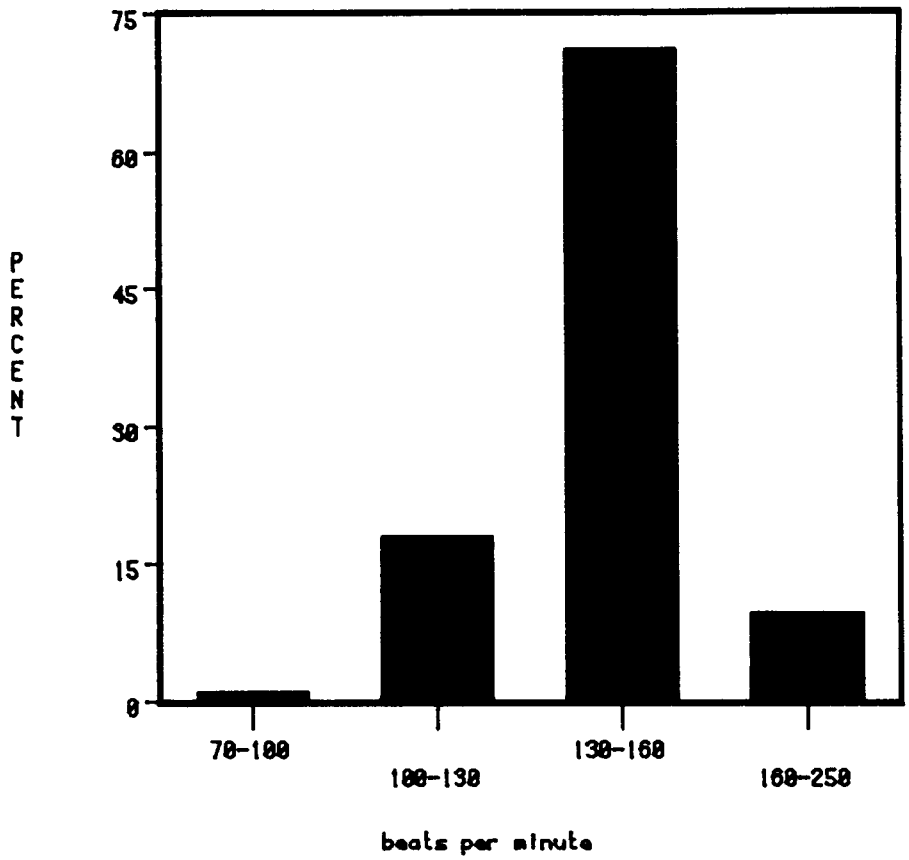


Figure 5.5 BLOOD PRESSURE

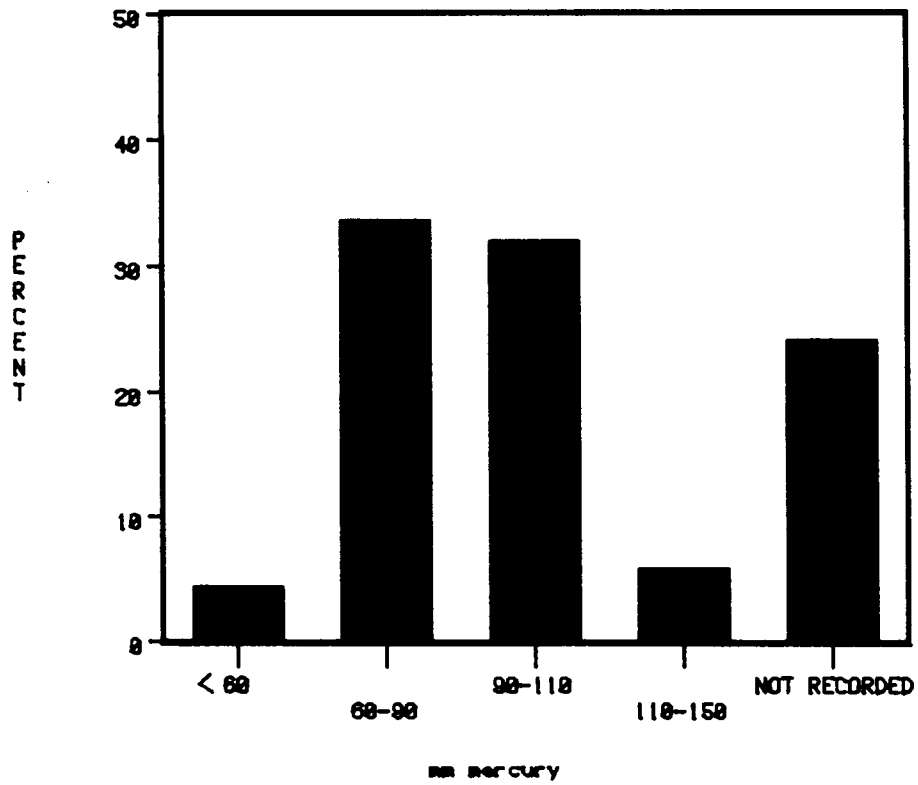


TABLE 5.3

PULSE RATE AND BLOOD PRESSURE

n = 143

PULSE RATE beats/min		BLOOD PRESSURE (mm mercury)			
		< 60	60 - 90	90 - 110	> 110
	TOTALS	24	183	174	32
< 100	4	-	1	2	1
100 - 130	72	2	18	48	4
130 - 160	295	13	147	110	25
> 160	42	9	17	14	2

Frank otitis media or suppurative ear disease was noted in 9,7 percent. Follicular tonsillitis was diagnosed in 2,9 percent. In the remainder (55 percent) the upper respiratory tract was normal.

5.2.9. Lower Respiratory Tract

This was clinically normal in 266 infants (48,8 percent).

Twenty one infants had lower airways obstruction presenting with a wheeze. Pneumonitis associated with tachypnoea and confirmed by the radiological finding of bilateral infiltration occurred found in 29 infants. Pneumonia with radiological evidence of consolidation was present in 26 infants (4,8 percent) of whom 6 were thought to have pulmonary tuberculosis on account of marked hilar adenopathy.

5.2.10 Heart

Six infants had a cardiac murmur regarded as significant. One was diagnosed as a patent ductus arteriosus and the others as small ventricular septal defects.

5.2.11 Abdomen

In the majority (96,5 percent) examination of the abdomen was entirely normal. Mild hepatosplenomegaly was noted in 10 patients but all had normal liver enzymes, were anicteric and had no other clinical manifestations of chronic liver disease.

An incomplete ileus with abdominal distension and decreased bowel sounds was found in 8 infants while one infant had a complete ileus. Ileus was a transient phenomenon resolving with rehydration and correction of any biochemical derangement.

5.2.12. Central Nervous System

This was normal on clinical examination in 441 patients (80,9 percent). Sixty eight infants (12,4 percent) were drowsy but had no other abnormal neurological signs. Excessive irritability was a feature of 11 infants but no neurological abnormality was found and the cerebrospinal fluid was normal in each case. One other infant who was extremely irritable on admission was found to have a bacterial meningitis due to klebsiella. Abnormal muscle tone was noted in 16 infants of whom 12 were hypotonic and 4 were hypertonic. None of these infants had any other neurological abnormality detected. Generalised convulsions shortly before or during the admission occurred in 8 infants. No neurological sequelae were evident at discharge in any of these infants. One had a serum sodium greater than 150 meq/l but in the remainder apart from a degree of metabolic acidosis there was no identifiable contributory metabolic upset.

5.2.13. Other Conditions

In 65 of the infants studied additonal diagnosis were made. These are shown in Table 5.4. Measles was the most frequent additional diagnosis but was not common with an overall incidence of 1,8 percent.

TABLE 5.4

OTHER CONDITIONS

DIAGNOSIS	NO OF CASES
Measles	10
Infantile eczema	6
Scabies	7
Rickets	9
Kwashiorkor	3
Salicylism	2
Cerebral palsy	2
Non accidental injury	2
Other specific conditions (one of each)	11
Inguinal hernia	
Morgagni hernia	
Retinoblastoma (ocular)	
Cleft palate	
Foetal alcohol syndrome	
Gastro-eosphageal reflux	
Rectal prolapse	
Conjunctivitis	
Hydrocephalus	
Acraniosynostosis	
Hirschsprung's disease	
Other non-specific conditions including:	13
Non-specific skin rashes	
Single café au lait spots	
TOTAL	65

5.3. INVESTIGATIONS

5.3.1. Acid-base Status

The acid-base status of all 545 infants is shown by Figure 5.6A, 5.6B and 5.6C. The pH was below the normal range in 97,2 percent (< 7,37) and markedly low (< 7,20) in 39,6 percent. In the majority of patients the standard bicarbonate was also low (< 19 meq/l) indicating a metabolic acidosis while in most (84,6 percent) the pCO_2 was below 37 mm of mercury indicating an element of respiratory compensation. In 38,2 percent the pCO_2 was significantly lowered (< 30 mmHg). An elevated pCO_2 (> 40 mmHg) indicating a failure to compensate for the metabolic acidosis was found in 6,8 percent.

In 196 infants the presence of tachypnoea was solely attributable to metabolic acidosis. Acidosis was diagnosed on clinical grounds alone in 255 (46,8 percent) infants. A comparison of this with the actual acid-base values is presented in Table 5.5. Seventy eight percent of infants thought clinically to be acidotic had a pH value below 7,3 while 62 percent of infants regarded as not acidotic, were found to have a pH of less than 7,3.

5.3.2. Serum Sodium

The distribution of serum sodium values is shown in Figure 5.7. Hypernatraemia (serum sodium > 150 mmol/l) occurred in 4,8 percent. Significant hyponatraemia (serum sodium < 125 mmol/l) was present in 3,3 percent and 13,6 percent had a serum sodium less than 130 mmol/l.

Figure 5.6A ACID-BASE STATUS (Standard bicarbonate)

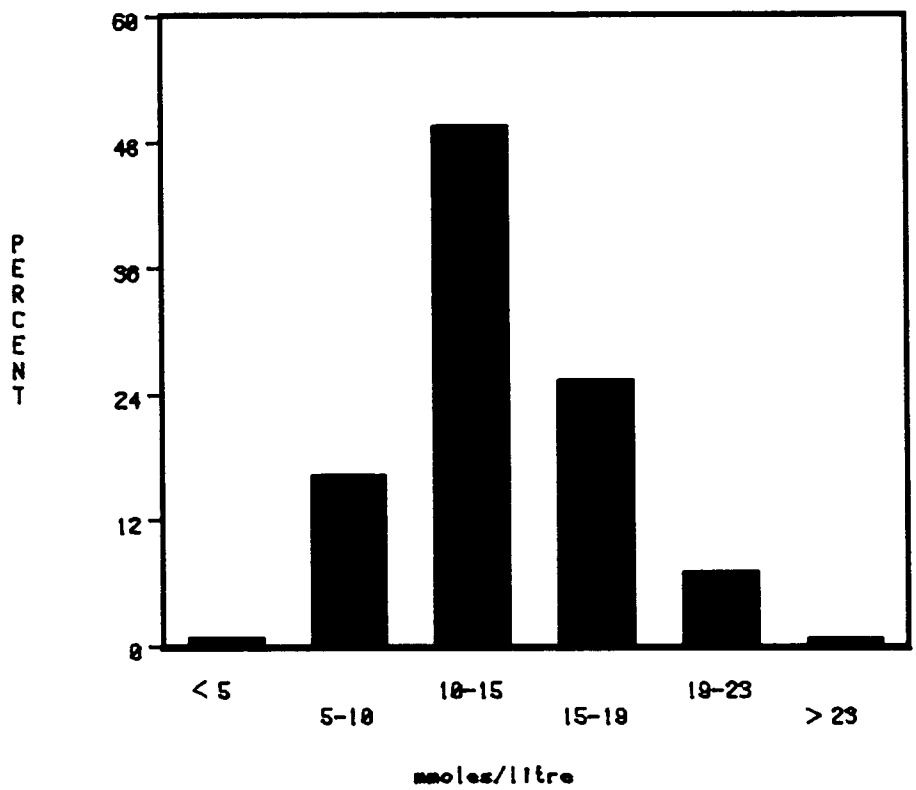


Figure 5.6B ACID-BASE STATUS

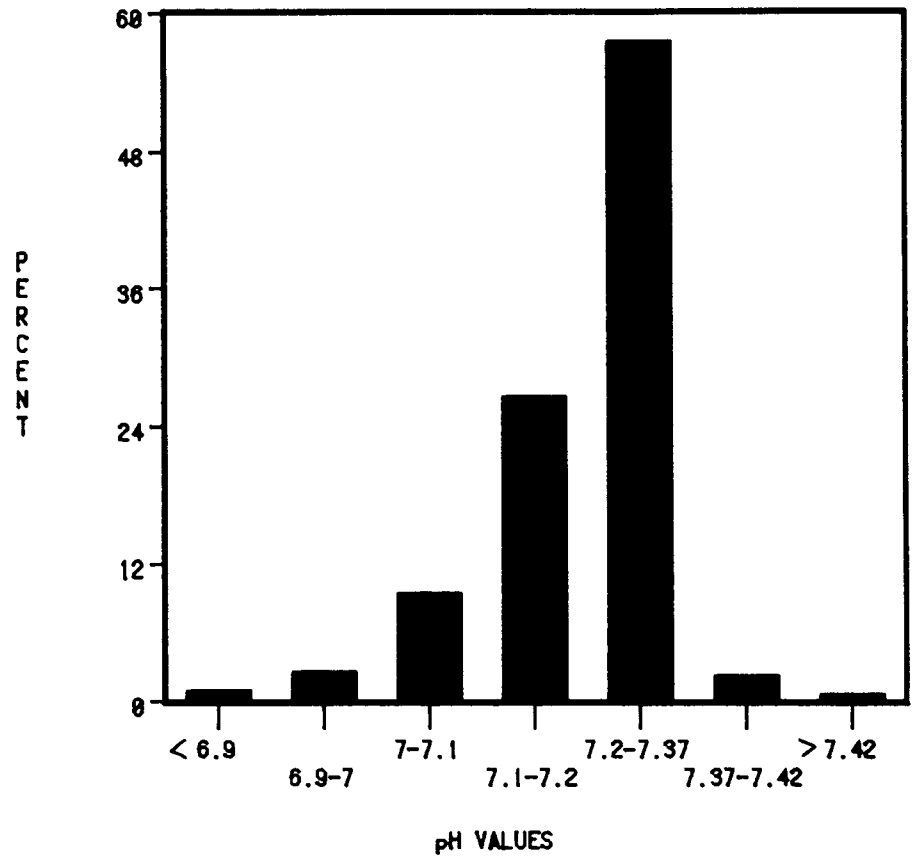


Figure 5.6C ACID-BASE STATUS (pCO2)

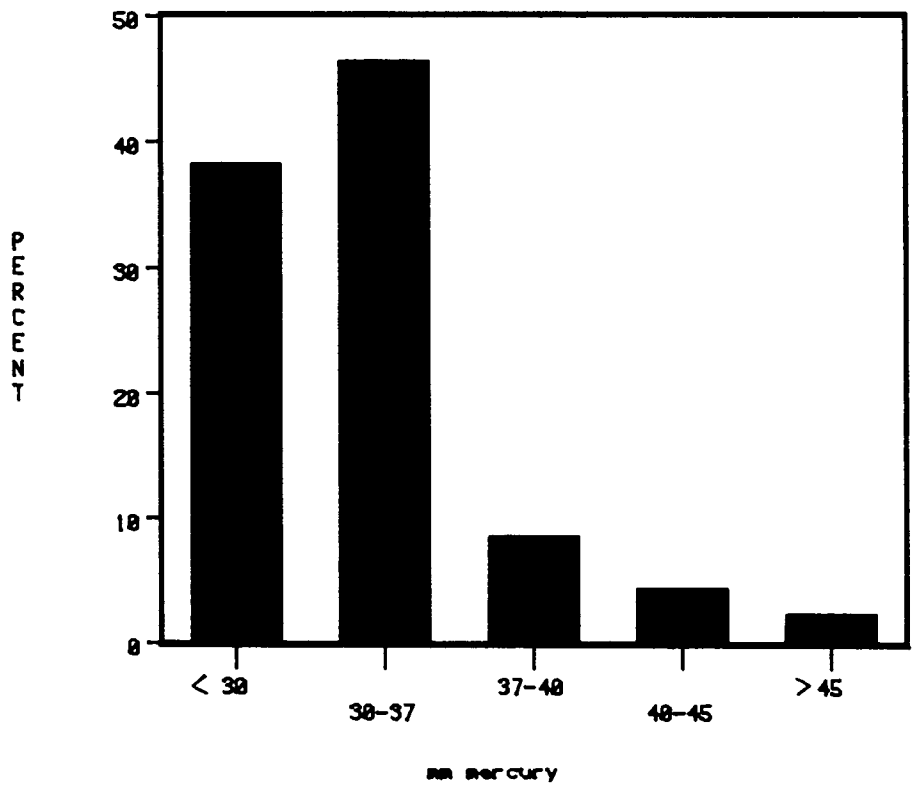


TABLE 5.5

COMPARISON OF CLINICAL ASSESSMENT OF METABOLIC ACIDOSIS WITH THE MEASURED VALUE

MEASURED pH VALUE	CLINICAL ASSESSMENT	
	ACIDOTIC	NOT ACIDOTIC
< 6,8	1,5%	-
6,8 -7,1	18,6%	3,1%
7,1 -7,2	24%	17,3%
7,2 -7,3	34,3%	41,8%
⩾ 7,3	21,6%	37,8%

Figure 5.7 SERUM SODIUM

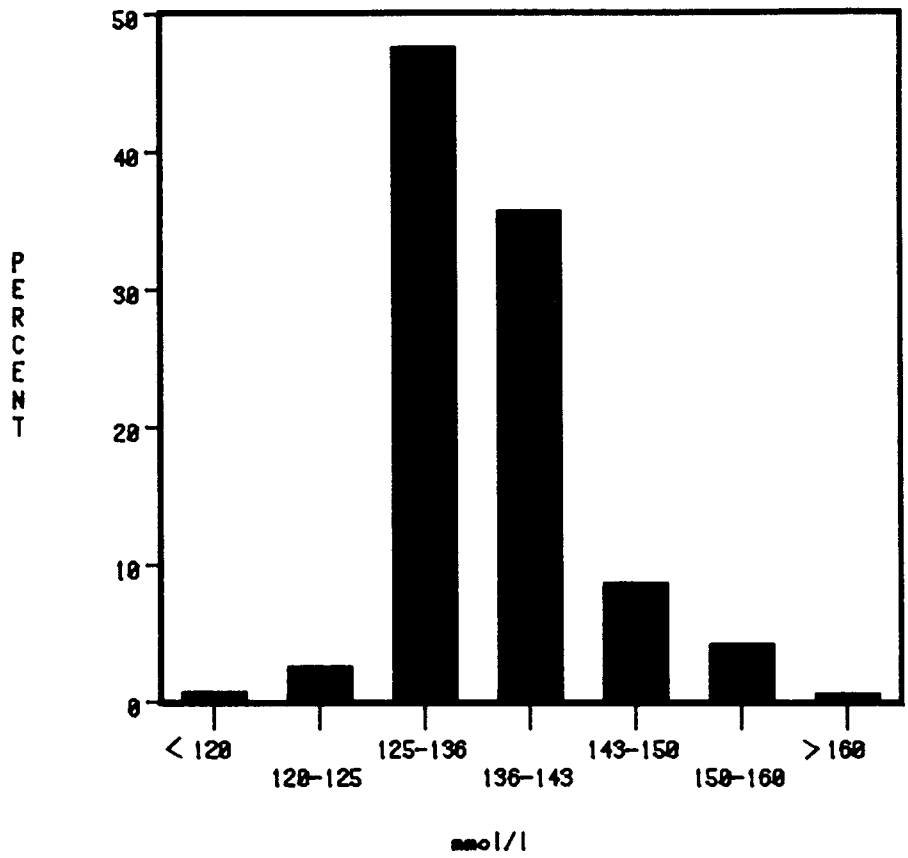
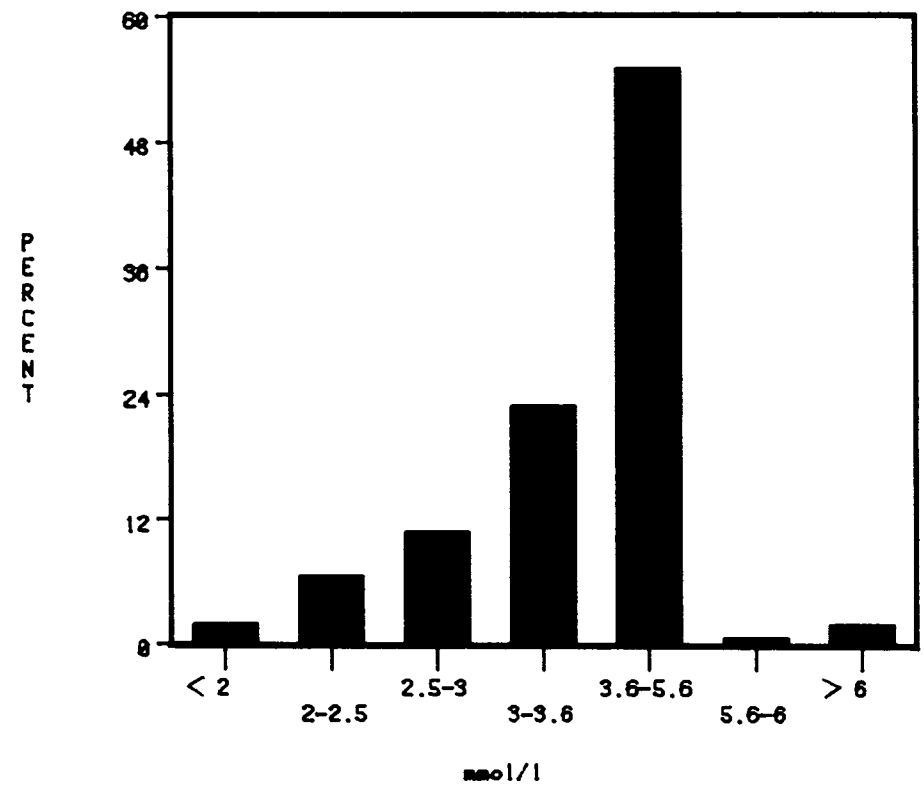


Figure 5.8 SERUM POTASSIUM



5.3.3. Serum Potassium

Hyperkalaemia (serum potassium > 6 mmol/l) was present in 2,1 percent while hypokalaemia (serum potassium < 3 mmol/l) occurred in 19,4 percent of the patient group. The distribution of serum potassium values is shown by Figure 5.8.

5.3.4. Serum Proteins

Total serum proteins and serum albumin were estimated on blood samples taken at the time of admission to the rehydration ward from 544 infants. As the majority of patients were dehydrated at this stage (Tables 5,1 : 5,2) the values are higher than expected for the normally hydrated infant. The range of results is shown in Figure 5.9. A serum albumin concentration of less than 35 g/l is accepted as indicating hypoalbuminaemia in normally hydrated children and was found in 27,2 percent of the samples tested. After rehydration an undetermined but a significant number of the group with results above 35 g/l could have been expected to fall below this level, increasing the incidence of hypoalbuminaemia. The majority of the measured albumin values (65,5 percent) ranged between 35 and 50 g/l.

5.3.5. Haemoglobin Concentration

Haemoglobin estimations were performed on 544 infants. For

Figure 5.9A SERUM PROTEINS (Total protein)

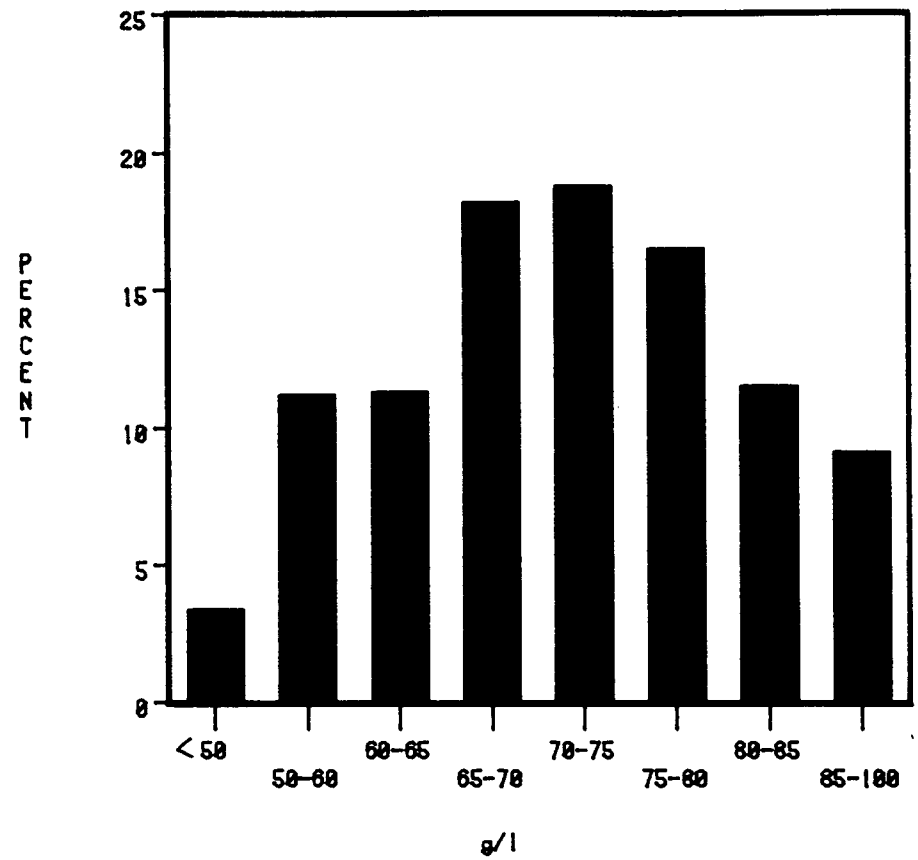
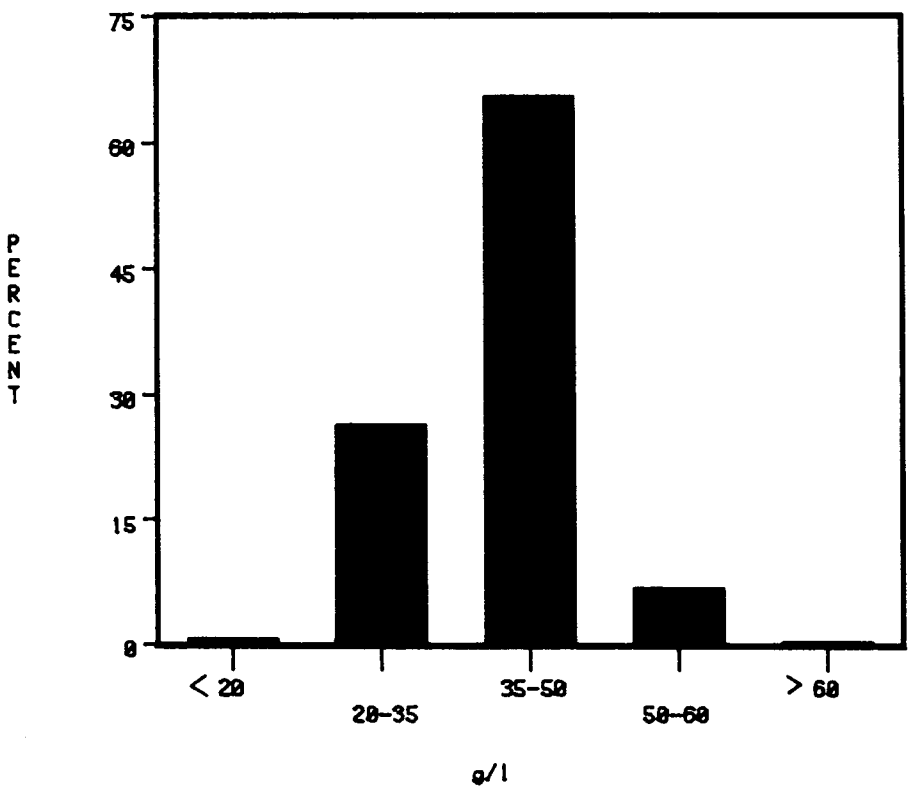


Figure 5.9B SERUM PROTEINS (Albumin)



the reasons outlined above the estimations in the majority were elevated above the true values due to the haemoconcentration of the specimens. A haemoglobin concentration below 9,5 g/dl is below normal ($>$ 2 standard deviations from the mean)[83] for adequately hydrated infants in this age range. In the patients studied 3,7 percent had a haemoglobin concentration below normal. The distribution of haemoglobin concentrations is reflected by in Figure 5.10.

5.3.6. Mean Corpuscular Volume (MCV)

A mean corpuscular volume of less than 70 fl (femto litres) is below normal for the age range of the infants studied[83]. The distribution values found is shown in Figure 5.11 and 131 infants (24 percent) had a mean corpuscular volume below normal. A tabulation of the haemoglobin concentrations versus mean corpuscular volume in shown in Table 5.6.

5.3.7. Total Leucocyte Count

The distribution of total leucocyte counts is shown in Figure 5.12. The normal range is from 6000 to 17000 cells per cubic millimetre (mm^3)[83] and 69,8 percent of the samples fell within these limits. Leukopenia was uncommon as only 2,8 percent had a leucocyte count below 4 000 cells per mm^3. In contrast a significant number (26,3 percent) had a leucocytosis with counts over 17 000 cells per mm^3.

Figure 5.10 HAEMOGLOBIN CONCENTRATION

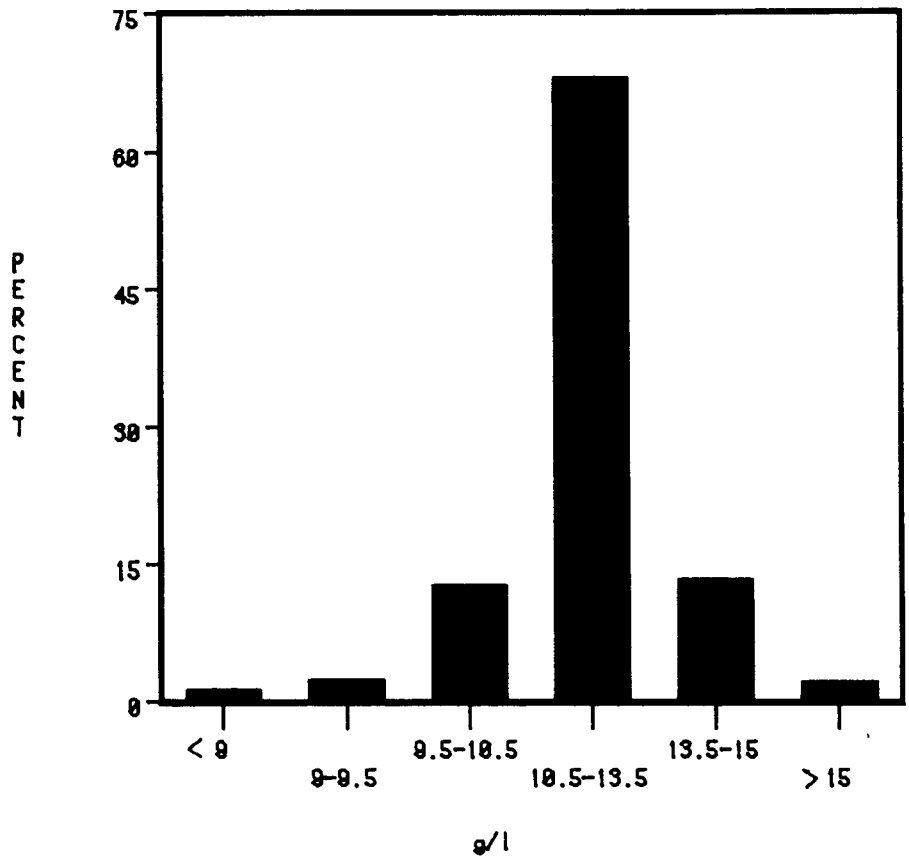


Figure 5.11 MEAN CORPUSCULAR VOLUME (MCV)

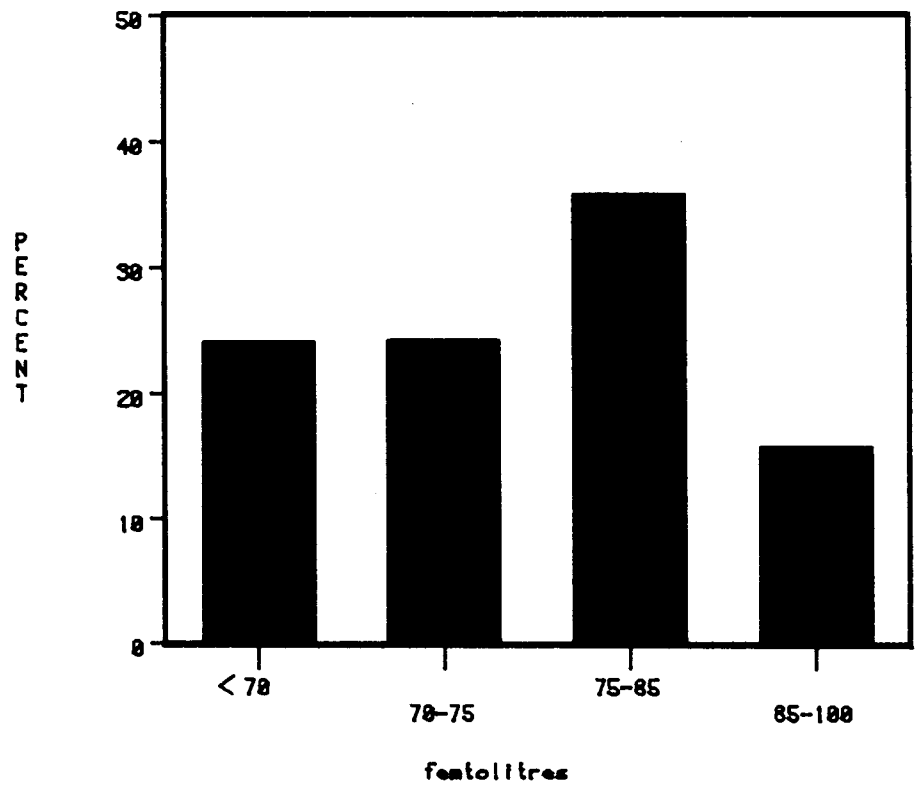
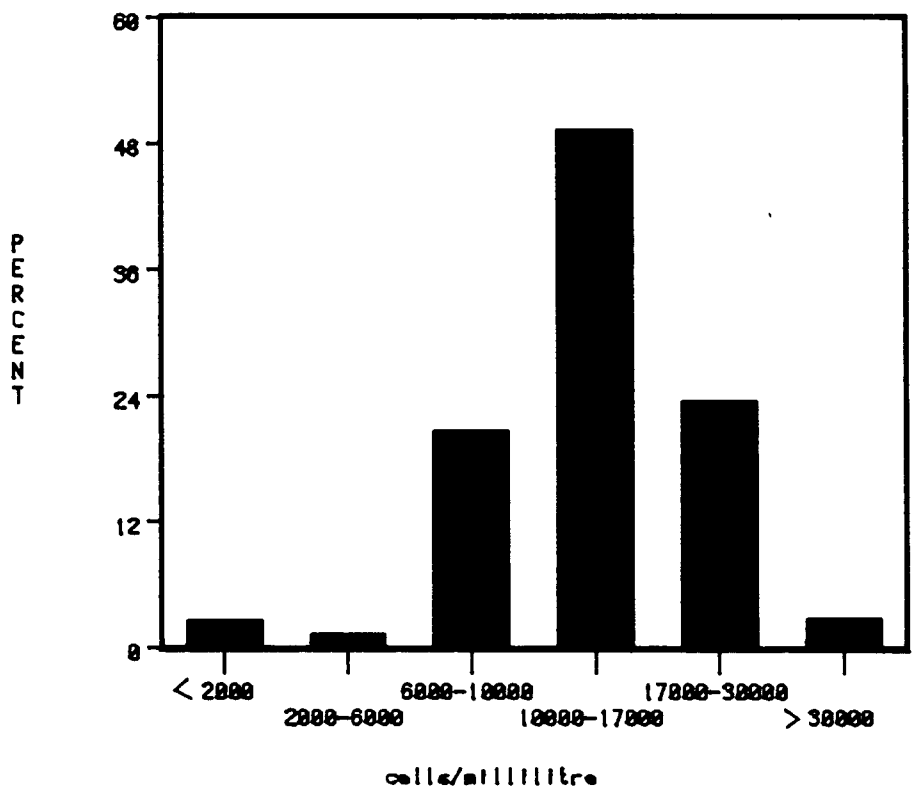


TABLE 5.6.

HAEMOGLOBIN CONCENTRATION VERSUS MEAN CORPUSCULAR VOLUME

		MEAN CORPUSCULAR VOLUME (MCV) (Femtolitres)			
		< 70	70-85	85-100	Totals
Haemoglobin Concentration (g/dl)	> 7	1	0	0	1
	7-9,5	7	10	2	19
	9,5-13,5	105	258	76	439
	> 13,5	18	59	8	85
	TOTALS	131	327	86	544

Figure 5.12 TOTAL LEUCOCYTE COUNT



5.3.8. Differential Leucocyte Counts

The differential leucocyte counts of the 532 blood smears examined are shown in Table 5.7. In many there was a reversal of the normal lymphocyte predominance of this age group. Eosinophilia was unusual with 0,6 percent having an eosinophil count greater than 10 percent of the total leucocyte count.

5.3.9. Peripheral Smears

A leftward shift in the polymorphonuclear leucocytes was noted on the peripheral smear in 40,2 percent while in 24,8 percent toxic granulations of the polymorphonuclear leucocytes were observed. Atypical lymphocytes were found in 7,1 percent of smears. Table 5.8 reflects the combinations found in the 532 peripheral smears examined.

5.3.10. Blood Cultures

Blood cultures were taken from each patient at the time of admission. In 26 patients (4,6 percent) these were positive with a growth of bacteria other than Staphylococcus epidermidis (regarded as a skin contaminant) present. As reflected in Table 5.9 16 infants had gram negative bacteria cultured but in only one infant did this appear of immediate clinical significance. One infant previously described with Klebsiella meningitis had a positive blood culture of the same organism. In the remainder of infants with positive blood cultures no specific treatment was instituted.

TABLE 5.7

DISTRIBUTION OF DIFFERENTIAL WHITE CELL COUNTS

	Percentage Total Leucocyte Count	Neutrophils	Percentage Total Leucocyte Count	Lymphocytes	
	< 20%	5,1%	20%	7,7%	
Normal[1,2] Range	20-40%	27,2%	20-40%	32,9%	
	40-50%	18,2%	40-50%	20,3%	
	50-60%	17,9%	50-60%	15,4%	Normal Range
	60-80%	25,8%	60-80%	21,4%	
	⩾ 80%	5,8%	⩾ 80%	2,3%	

1 Philip Lanzkowsky. Pediatric Hematology-Oncology. McGraw-Hill Inc. New York 1980, p.224-229

2 W J Williams, A S Schneider. Examination of the peripheral blood. Chapter 2 In: Hematology Eds W J Williams, E Beutter, A J Erslev, R W Rundles. McGraw Hill Inc, New York 1972, p.18.

TABLE 5.7

MONOCYTES AND EOSINOPHILS

	Percentage Total Leucocyte Count	Monocytes	Percentage Total Leucocyte Count	Eosinophils
Normal Range[1,2]	< 10%	87,2%	< 10%	99,4%
	10-15%	9,2%	10-15%	0,2%
	15-20%	2,8%	15-20%	0,2%
	>20%	0,8%	>20%	0,2%

1 Philip Lanzkowsky. Pediatric Hematology-Oncology. McGraw-Hill Inc. New York 1980, p.224-229

2 W J Williams, A S Schneider. Examination of the peripheral blood. Chapter 2 In: Hematology Eds W J Williams, E Beutter, A J Erslev, R W Rundles. McGraw Hill Inc, New York 1972, p.18.

TABLE 5.8

PERIPHERAL SMEARS

LEUCOCYTES on PERIPHERAL SMEAR

	N	%
Normal	299	56,2
Toxic Granulations	13	2,4
Left Shift	75	14
Toxic Granulations and Left Shift	107	20,1
Toxic Granulations, Left Shift and Atypical Lymphocytes	19	3,5
Toxic Granulations and Atypical Lymphocytes	6	1,1
Left Shift and Atypical Lymphocytes	13	2,4
TOTAL	532	100

TABLE 5.9

BLOOD CULTURES

n = 544

	N		%
No Growth	389		71,5
Contaminant growth only (Staph epidermidis)	130		23,9
Salmonella	4		
Campylobacter	4		
Klebsiella	6	25 Significant Growth	4,6
Escherichia coli	2		
Streptococcus	8		
Pneumococcus	1		

5.3.11. Urinalysis

Urine was not tested in 144 infants. These were mostly female infants or those in whom perineal excoriation precluded the adequate application of a urine bag. A total of 401 urine specimens were examined (Table 5.10) and no abnormality found in 337 (84 percent). Urinary tract infection diagnosed by a pure growth of a single organism and more than 10 white cells per high power field was found in 14 infants (3,5 percent). Repeat urinalysis to confirm the diagnosis was not undertaken as part of this study. A further 36 infants had either greater than 10 white cells per high power field or a pure growth of a single organism on culture indicating a possible urinary tract infection. Granular casts were a common finding on urine microscopy.

5.4. COURSE IN THE REHYDRATION WARD

5.4.1. Medication

All infants admitted to the rehydration ward receive oral potassium supplementation in the form of a 10 percent potassium chloride solution unless there is hyperkalaemia or evidence of impairment of renal function. Apart from the oral potassium 311 infants (57 percent) received no other medication. Forty percent (Table 5.11) received an antibiotic and the most frequently prescribed combination was oral or intravenous penicillin and cotrimoxazole. This was given to 102 patients (18,7 percent). A further 81 patients (14,9 percent) received penicillin alone.

TABLE 5.10

URINALYSIS

n = 401

No abnormality		337
White cells	< 10/HPF	8
(WBC)	> 10/HPF	13
Escherichia Coli		19
+ < 10 WBC/HPF		3
+ > 10 WBC/HPF		10
Klebsiella only		4
+ > 10 WBC/HPF		4
Contaminated		3

TABLE 5.11

MEDICATION GIVEN DURING ADMISSION TO THE REHYDRATION WARD

	N	%
NO MEDICATION	311	57%
ANTIBIOTICS		
Penicillin* alone	81	
Penicillin* + Cotrimoxazole[1]	102	
Penicillin* + Gentamicin[2]	16	40,2%
Penicillin* + Other antibiotic[1]	2	
Amoxycillin*	13	
Other Antibiotics[2]	5	
OTHER MEDICATION		
Oral "Cocktail"[1] (Gentamicin, Metronidazole Cholestyramine)	6	
Metronidazole[1]	3	2,8%
Mebendazole[1]	3	
Other Medication[1]	3	

* Intravenous or oral

1 Oral

2 Intravenous

Indications for the use of antibiotics, when given in the patient records, were upper respiratory tract infections (most frequent), otitis media, tonsillitis or pneumonia. A cocktail of Gentamicin (50 mg/kg body wt/day 4 hourly), Metronidazole (100 mg 8 hourly) and Cholestryamine (1g 6 hourly) all administered orally was used to treat ongoing diarrhoea in 6 patients during their stay in the rehydration ward.[20,62]

5.4.2. Duration of the Stay in the Rehydration Ward

As reflected by Figure 5.13, infants spending 2 or fewer days in the ward constituted 64,5 percent of the total. A further 16,8 percent were admitted for 3 days while the longest stay was one infant who spent over 10 days in the rehydration ward.

5.4.3. Disposal from the Rehydration Ward

Most patients (79,4 percent) were discharged home (Table 5.12). The mothers received instructions to visit the local day hospital (most), clinic or the outpatients department of the Red Cross Children's Hospital within 24 hours for a check of hydration. Transfer to a inpatient hospital ward from the rehydration ward was necessary in 95 instances and of these 79 were admitted to an inpatient ward in the Children's Hospital. Most admissions occurred after the infant had been in the rehydration ward for 2 or more days. The early admissions (i.e. within the first day) were necessitated either because of the poor clinical state or the very young age of the infant.

Figure 5.13 STAY in the REHYDRATION WARD

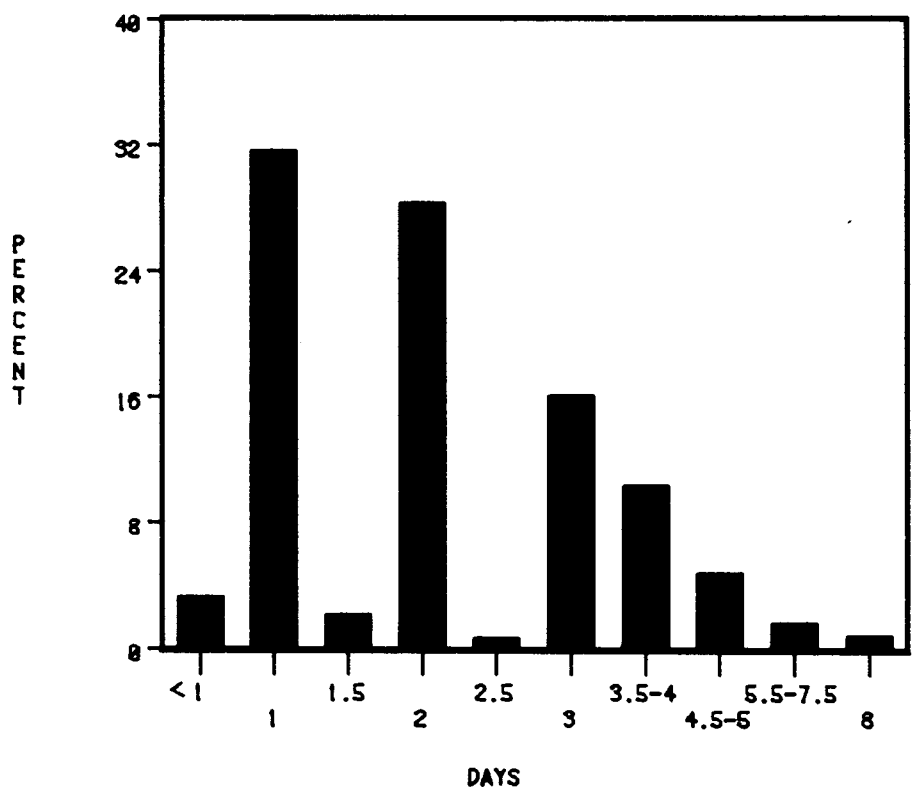


TABLE 5.12

STAY IN THE REHYDRATION WARD

DESTINATION AFTER DISCHARGE	TOTAL	STAY IN DAYS						
		< 1	1	1,5	2	2-4	4-7,5	> 7,5
Home	433 (79,4%)	8	159	12	137	94	19	4
Hospital Wards Children's Hospital	79 (14,5%)	6	3	-	13	44	12	1
Other Hospitals	16 (2,9%)	3	2	-	1	7	3	-
Absconded from Rehydration ward	16 (2,9%)	-	8	-	3	4	1	-
DIED	1 (0,2%)	1	-	-	-	-	-	-
Patients	545	18	18	12	154	149	35	5

Despite overcrowded conditions, particularly in the summer months, the number of mothers absconding with their infants from the rehydration ward before discharge was very small.

One child died shortly after admission to the rehydration ward following a respiratory arrest with refractory shock not responding to active resuscitation. The mortality rate of patients in the rehydration ward was thus very low (0,2 percent).

5.5. COURSE AFTER DISCHARGE FROM THE REHYDRATION WARD

5.5.1. Duration of Hospitalization after Transfer from the Rehydration Ward

As described in paragraph 5.5.3, 95 infants were transferred to other wards. The duration of hospital stay ranged from 5 to over 30 days (Table 5.13). Most (79,7 percent) were hospitalised for more than 10 days but 62,8 percent were discharged in less than 20 days.

5.5.2. Subsequent Course

The hospital records were reviewed for all 545 infants included in the study after a period of not less than 6 months from discharge. Sixteen had not reattended the hospital and their subsequent course was unknown. In the remainder many had attended the outpatients' department on several subsequent occasions. Readmission to the rehydration ward due to a further

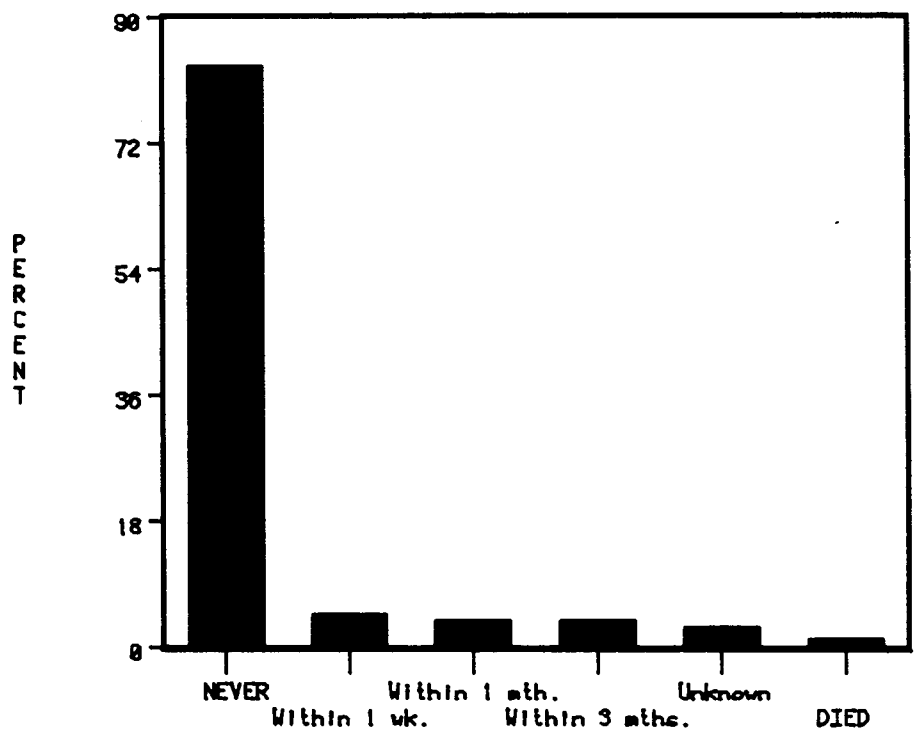
episode of dehydrating diarrhoea was necessary in 84 cases (15 percent). A further 7 infants had died since discharge, apparently from dehydrating diarrhoea. One infant died of a Klebsiella meningitis (see above) and in this patient the organism with a similar pattern of antibiotic resistance had been cultured in the urine and blood (see above) during his admission to the rehydration ward. The overall mortality in the patient group, including all deaths recorded, was 1,5 percent. Figure 5.14 reflects the subsequent course of the infants studied after their discharge.

TABLE 5.13

DURATION OF HOSPITALISATION n = 95

Length of hospital stay	% patients hospitalised
< 5 days	9,3
5-10 days	10,5
10-20 days	43
20-30 days	20,9
> 30 days	16,3

Figure 5.14 COURSE AFTER DISCHARGE



DISCUSSION

The role of diarrhoea in the "diarrhoeal disease - protein energy malnutrition diathesis" is of great interest. It is clear that diarrhoea is a frequent occurrence in malnourished infant populations[118]. Of particular importance is whether undernutrition results predominantly from an inadequate dietary intake or whether recurrent episodes of diarrhoea compromise the digestion and absorption of a otherwise adequate protein and calorie intake[135]. Both probably play an role in underdeveloped areas. Depending on which is more important the type of intervention will differ both for the individual infant and in the wider community context. In this study 32 percent of the infants were under 80 percent of expected weight (i.e. underweight for age N.C.H.S. values)[57] and 6,3 percent were below 60 percent of expected weight for age (Marasmic) (Figure 5.1). In a comparable group of 258 Malaysian infants Manderson[89] found 29,3 percent underweight for age and 4,3 percent marasmic. Including all 327 children aged from birth to 7 years in her study, 47 percent were underweight for age and 7 percent marasmic. Schoub et al[132] in their study of 37 Black infants from Johannesburg aged less than 2 years old found 56 percent to have weights below 80 percent of expected weight for age. Freiman et al[48] in another comparable study of 191 infants and 178 age matched controls showed 48 percent of the patients to be underweight compared with 22 percent of the controls.

Bowie[19] reported that the majority of non-white infants admitted to the "rehydration ward" at the Red Cross Children's Hospital (Cape Town 1960) were well below the third Boston percentile and that this discrepancy increased with advancing age, particularly in the second

year of life. Wittmann and Hansen[159] in a further study at the Children's Hospital (1965) of 101 non-white children with diarrhoea mostly less than 18 months of age, found 63,4 percent with weights below the third Boston percentile. The trend away from the normal weight range for age was again more marked with advancing age. At 3 months or less the mean percent expected weight was 85 $\pm$ 4 percent while over 15 months this had dropped to 69 $\pm$ 4 percent. In their study the majority of the controls were normally nourished and none were marasmic, compared to a 9,9 percent incidence of marasmus in the infants with diarrhoea. A study by Willoughby et al[158] of children attending the outpatients department of the Children's Hospital in 1972 and 1973 irrespective of diagnosis, showed that 22,5 percent of Coloured infants and 20 percent of Black infants below one year had weights less than 80 percent of the expected value.

In the current study all the patients were aged between 6 weeks and 1 year and correspond to the younger infants reported in the studies quoted above. The majority (68,2 percent) were normally nourished, indicating that in the young infant with diarrhoeal disease, malnutrition is a less important factor in the pathogenesis of the disease. As mentioned in Chapter 4 a birthweight less than 2,5 kg was significantly associated with infants who were underweight for age (x^2 46,4 $p < 0,0001$). Sixteen percent of infants in the present study had a low birthweight and 32 percent were underweight for age. This suggests that in half prenatal and intrauterine factors influenced later body mass.

The control group was of an equal nutritional standard (Figure 5.1) in contrast with the control groups discussed above who were better

nourished than the patients. The patients and control infants in the current study are of a similar nutritional state to the controls in the study of Wittman and Hansen[159]. They are less well nourished than the infants in the more recent study by Willoughby et al[158] at the Children's Hospital (Figure 5.2). This discrepancy may be explained by the inclusion of some white infants (7 percent) in their study or by some lowering of the overall nutritional status since 1972-1973 of infants attending the Children's Hospital.

Diarrhoeal disease seen in the Rehydration ward occurs in a relatively well nourished infant population during the first year of life. This suggests that diarrhoea is the important initiating factor in the "diarrhoeal disease - protein energy malnutrition diathesis". The trend of increasing malnutrition with advancing age outlined in the studies discussed above further supports this contention. The disturbance in protein, fat and carbohydrate absorption[94] that results during and after an episode of diarrhoea may with borderline intake be the deciding factor in the initiation of the malnourished state. Nazer[108] states that a global improvement of nutrition is essential to break the link between diarrhoea and nutrition. It may well be that in the infant the converse applies. Prevention or amelioration of episodes of diarrhoea will remove a major precipitating factor of malnutrition . Some longitudinal cohort studies showing that diarrhoea directly causes malnutrition support this hypothesis[30.95]. Diarrhoea is a more potent cause of malnutrition than other diseases (excluding malaria) in developing countries[30,95,122]. Growth rates amongst infants with a high prevalence of diarrhoeal disease are significantly lower than those with a lower frequency of diarrhoea[95]. These weight deficits are only

partially reversed by protein and calorie supplements. From data available it cannot be conclusively proved that acute infectious infantile diarrhoea is the major factor precipitating malnutrition. This study and the others quoted suggest this is so but further prospective longitudinal studies concentrating on this age group are necessary. It may be that if diarrhoea can be prevented or reduced in frequency at an early age the spiral of increasing malnutrition and diarrhoea will be broken. The prevention of early malnutrition is important particular in view of the findings of Stoch and Smythe[145] which show that it may ultimately predjudice intellectual development.

The equal sex distribution of patients in the current study differs from the findings of others[43,70,108,112,157] who have shown that male infants have a greater disposition to develop diarrhoeal disease. This difference is most marked in the first 3 months of life[1,112,144] but although the current study included 118 infants under 3 months of age there was no significant difference in the sex incidence. The age distribution in the patient group was similar to that of previous studies from Cape Town[19,159] with infants (33,8 percent) from 3 to 6 months of age (Figure 5.2) being most frequently affected. Nazer[108] in his review of acute diarrhoea in the developing world reports that the peak age incidence is between 6 months and a year. In the current study the infants had a median age of 5 months and a mean age of 5,6 months. Mutanda[104] in Kenya and Freiman[48] in Johannesburg report a similar age distribution to the current study. Since over 60 percent of the patients admitted to the rehydration ward are under one year of age and more than half of these (55,5 percent) are under 6 months, it is clear that diarrhoeal disease is a particular problem of the young infant in this area.

The clinical picture of the patient group as a whole was unremarkable. The duration of diarrhoea prior to admission ranged from less than 48 hours (21,5 percent) to over 10 days (3 percent) with 68 percent having had diarrhoea for 4 days or less. Evans et al[42] in a study of infants (mean age 10 months) in Mexico City report that the median duration of diarrhoea at presentation was 4 days with a range of 1 to 25 days. Pickering et al[110] in their study from Houston and Mexico found that 78 to 90 percent respectively had had diarrhoea for 1 to 4 days before admission.

In the current study the onset of diarrhoea was usually sudden with copious watery stools. When vomiting occurred the onset invariably coincided with that of the diarrhoea although 23 percent had diarrhoea without any significant vomiting. Non-specific associated symptoms particularly cough, fever and coryza were not infrequent as was general irritability which occurred in most infants. Convulsions were uncommon, reported in only 6 infants and associated with fever in 5. The non-specific nature of the presenting history is in keeping with published surveys of infantile diarrhoea[43,88,144]. A majority (75 percent) of the infants in the current study had no history of a previous admission for diarrhoea which reflected in part the young age of the infant population studied.

Management of these patients prior to admission was inadequate. Almost half had received no specific treatment and oral rehydration therapy was not commonly used. Oral antibiotics and antidiarrhoeal medication prescribed by the family doctor were given to 14 percent. The small number attending either a local clinic (19,6 percent) or a hospital outpatients department (12,3 percent) were often given Darrow's solution

or Rehidrat® (a commercially prepared glucose and electrolyte solution) in place of normal feeds. The use of Traditional remedies was not often admitted by the Black parents. It must be accepted that there is a reluctance to admit to this alternative therapy and the use of traditional remedies is probably more prevalent than found in this study. While there is considerable controversy regarding the correct composition of oral rehydration solutions[18,63], more specifically the sodium concentration, it is undoubtedly a successful method of management if initiated early in that it reduces morbidity and mortality[63,105,127]. Home-based oral rehydration programs have not been widely propagated in the areas from which the study patients orginate and this is borne out by the results of this study. As already noted in previous chapters this may be a valuable and effective method of reducing the number of admissions particularly amongst the Black infant population.

The results of the physical examinations serve to characterise the study group as do the results of the additional investigations performed. Only those which merit further discussion and comparison with other published work will be discussed. Not unexpectedly a significant number of patients were dehydrated 5 percent or more but of note was the discrepancy between the clinically estimated degree of dehydration and that calculated from the "dry" and rehydrated body weights. There was a tendency to clinically overestimate dehydration in infants with less severe dehydration (Table 5.2) which is probably accounted for by the setting in which the infants were examined. With more severe dehydration the tendency was to clinically underestimate the degree of dehydration. In the majority the error was within 2,5 percent of the calculated value and calculation of fluid requirements would not have

been significantly affected by this error. In a few the error was 10 percent or more but no major problems were encountered with intravenous rehydration. It is likely that renal compensation with an unnoticed increase or decrease in urine output occured in these cases. Shocked infants were regarded as 15 percent dehydrated and this may account for some who on calculation were significantly less dehydrated. These findings reinforce the view that changes in bodyweight are the only accurate method of determining the degree of dehydration. This is not possible in the majority of cases and clinical assessment remains important. Despite the errors demonstrated no problems related to intravenous rehydration based on clinical assessment occurred in the patients studied. Frequent reassessment as practiced in the rehydration ward would have identified initial clinical misassessment of the degree of dehydration.

Inaccuracies were also shown in the clinical assessment of the degree of metabolic acidosis with 21,6 percent of those thought to be clinically acidotic having a pH greater than 7,30. In contrast 20,4 percent of those assessed as not acidotic in fact had a pH below 7.20 (Table 5.4). It is possible that in some cases tachypnoea due to respiratory disease was attributed to the presence of metabolic acidosis. Since acid-base estimations are performed routinely in the drip room these errors were not important. The findings emphasize that in small infants the clinical signs of metabolic acidosis are not reliable.

An analysis of the clinical findings in relation to specific enteropathogens is presented in Chapter 7. Overall these findings were nonspecific reflecting diarrhoeal disease as seen in young infants. Fever occurred in 29,2 percent. Involvement of the respiratory tract

was common and was most often attributed to a viral infection of the upper (20,6 percent) and lower (9,2 percent) respiratory tract. Ironside et al[70] in a study of 339 cases of infantile diarrhoea found associated respiratory tract infection in 19 percent. Lewis et al[87] in a study of 152 children with diarrhoea mostly under 2 years found evidence of respiratory infection was often associated with the presence of rotavirus.

Other disease such as lobar pneumonia, (26 infants) urinary tract infection (14 infants), measles (10 infants) and meningitis/septicaemia (1 infant) was diagnosed in 9,4 percent. These could be regarded as parenteral factors in the aetiology of diarrhoeal disease. The significance of ear pathology (more particularly the middle ear) was difficult to assess as the clinical diagnosis of otitis media is subjective. In the current study the tympanitic membrane was often red on initial examination but appeared normal on examination the next day. In several instances bilateral otitis media was suspected on the basis of redness of the eardrums in a crying child. No abnormality was evident on repeat examination once the infant had stopped crying. Chronic suppurative otitis media constituted a significant fraction of ear disease diagnosed and its role in acute diarrhoea is unclear. The role of chronic ear disease in intractable diarrhoea of infancy has been highlighted by two recent papers[24,124]. Salazar De Sousa et al[124] showed latent, clinically inapparent otomastoiditis in 9 of 16 infants (mean age 41 days) and in 5 of these infants there was a dramatic improvement of the diarrhoea following surgical exploration of the mastoid and middle ear. While acute bacterial otitis media may indeed cause diarrhoea ear pathology was not included amongst the parenteral factors because of the difficulty in confirming this

diagnosis. Tonsillitis, acute and chronic otitis media and ear disease were noted in 12,6 percent of the patients.

Convulsions were uncommon occurring in only 8 patients (1,5 percent) and all were without sequelae. Three had a body temperature of 38°C or greater at the time of admission. Although some were younger than the accepted age range for febrile convulsion[2,46] it seems likely that the pyrexia was a contributory factor. In addition one was hypernatraemic. Other findings included ileus in 9 infants (incomplete in 8), abnormalities of muscle tone in 16 and a miscellany of mostly non acute conditions as reflected in Table 5.5.

Blood cultures were performed in all cases and a growth of potentially pathogenic micro-organisms was present in a minority (4,6 percent). Blood cultures were of little immediate relevance to the management of the patients as the results were available only 24 to 48 hours after admission. A bacteraemia associated with diarrhoeal disease is uncommon but when it occurs some interesting facts emerge. In the 8 patients with enteropathogens isolated from the blood 7 had similar microorganisms in the stool culture (4 Salmonella group B and 3 Campylobacter fetus jejuni). Only 2 of these patients received antibiotics (Penicillin and Cotrimoxazole) while in the rehydration ward but 4 of the 8 were admitted to a hospital ward because of ongoing diarrhoea. This was more frequent than the overall admission rate of 17,4 percent suggesting that the presence of these enteropathogens in the blood was predictive of persistent diarrhoea. Only enteropathogens found to have a significant association with diarhhoea in the current study (Chapter 6) were isolated from the blood cultures. These bacteria seem more likely to be invasive. As half the stool cultures (49,4

percent) contained a "significant" enteropathogen (see Chapter 6) and the majority of blood cultures were sterile it would appear that entero-invasion and resultant bacteraemia is an unusual feature in infantile diarrhoea. It must be remembered that this study reflects a relatively well nourished infant population.

One patient with a growth of Klebsiella from the blood culture had the same organism cultured from the urine and cerebrospinal fluid. In another 5 infants a growth of Klebsiella on the blood culture seemed of no consequence. Three of the 8 patients from whom Streptococci were isolated from the blood culture required admission for persistent diarrhoea. In one infant a growth of Streptococcus pneumonia appeared of no significance as did the culture from another of Escherichia coli on two occasions. It is possible that some of these microorganisms were skin contaminants as a number of the blood cultures contained Staphylococcus epidermidis (23,9 percent) indicating contamination from the skin despite reasonable antiseptic techniques (Table 5.9).

The acid-base and electrolyte abnormalities found are in keeping with the disease process. Most infants had a metabolic acidosis with some respiratory compensation (84,6 percent) compatible with the degree of dehydration present in most. In the current study 4,8 percent had a serum sodium greater than 150 mmol/l. Hill[61] in a study of hypernatraemic dehydration over a one year period at the Children's Hospital found an incidence of 3,8 percent in infants with acute diarrhoea. Beatty et al[6] in a study of 80 undernourished infants with acute diarrhoea at the same institution found hypernatraemia in 6,3 percent. Significant hyponatraemia ($Na^+ < 125$ mmol/l) occurred in 3,3 percent compared with the 5 percent incidence found by Beatty et al.

Samadi et al[125] in a study of 1330 children in Bangladesh under 3 years of age with diarrhoea report hypernatramia in 6,4 percent and hyponatraemia (defined in their study as $Na^+ < 130$ mmol/l) in 20,8 percent. This compares with 13,6 percent below that level in the current study and 24 percent in the study of Beatty et al[6]. The findings in the current study correspond with that reported in developing countries[63,125] with a low incidence of hypernatraemia and an intermediate incidence of hyponatraemia. The lower incidence of hynonatraemia may be explained by the relatively well nourished nature of the infants studied.

In the current study 19,4 percent of the infants were hypokalaemic ($K^+ <$ 3 mmol/l). A metabolic acidosis which may elevate the serum potassium was present in 84,6 percent of the infants studied. The serum potassium in addition does not reflect total body potassium[93] and for these reasons the actual incidence of potassium deficiency was probably much higher. All these infants received potassium supplementation unless contra indicated by evidence of renal insufficiency or hyperkalaemia. Hyperkalaemia ($K^+ > 6$ mmol/l) was uncommon occurring in only 2,1 percent and as shown in a previous study[6] potassium supplementation is safe provided that the dosage does not exceed 6 mmol/kg/day.

Serum albumin levels are of interest as there is a strong correlation between low values (< 35 g/l) and low weight for age in infants and young children[159]. Taking into account that these specimens were taken when the majority of the infants were dehydrated a significant number (27,2 percent) were hypoalbuminaemic. After rehydration it is likely that the number who were hypoalbuminaemic was higher. Beatty et al[6] found hypoalbuminaemia in over 75 percent of their 80 patients

over half of which were underweight for age. Mann et al[94] have shown that protein losses are very significant in acute diarrhoea and this finding is supported by the work of Mäki et al[91]. The patients in this current study were reasonably well nourished as judged on anthropometric grounds and acute protein loss may have contributed significantly to the low albumin levels. The results of the current study reflect a better nourished population with acute diarrhoeal disease than previous studies at the Children's Hospital[6,159]. This is possibly due to the young age of the infant sample.

Haemoglobin concentrations like the protein estimations were elevated on account of dehydration and haemoconcentration. A more valid estimation of the degree of iron deficiency was the mean corpuscular volume (MCV) which was below 70 fl in 131 infants (24 percent). The wide spread of values of haemoglobin concentration in patients with a similar MCV is most likely due to varying degrees of dehydration and haemoconcentration (Table 5.6). In view of the frequency of severe dehydration, metabolic acidosis and accompanying infections it is perhaps surprising that a leukocytosis was found in only 26,3 percent on admission. As a nonspecific response to stress of various kinds it is of limited value in the management of infants with diarrhoeal disease. Indeed leukopenia which was an infrequent finding (2,8 percent) is probably a more ominous sign. Of the 15 patients with leukopenia ($< 4,000$ cells/mm^3) 4 were admitted with persistent diarrhoea. In view of the small numbers it is not possible to draw any conclusions from this. Reversal of the normal lymphocyte predominance in the differential white cell count, a common finding (Table 5.7) and the left shift of the granulocyte series in 40 percent are further indicators of stress. Toxic granulations were present in the neutrophils in 26 percent of the smears examined. In

infants there is a tendency to release immature granulocytes into the circulation in response to stress, be it infection, metabolic upset, shock or other disease processes[83]. The result is a leukocytosis, often marked, with a left shift and this is a nonspecific sign. This probably accounts for the few very high white cell counts (> 30,000 cells/mm^3) seen in this study (Figure 5.12). Toxic granulations are a non-specific feature of severe infection or other toxic states[83].

Atypical lymphocytes are a feature of infection particularly viral infection but may also occur with other conditions. If they form more than 20 percent of the white cells on the peripheral smear they are suggestive of conditions such as infectious mononucleosis, infectious hepatitis, cytomegalovirus infection or drug hypersensitivity. In the patients studied 7 percent had atypical lymphocytes on the peripheral smear (all < 20 percent of total white cells) probably indicative of a viral infection. This is relatively low if the incidence of presumed viral infections of the respiratory tract is taken into account. The relationship of the total white cell count, differential count and abnormalities on the peripheral smear to the enteropathogens isolated in the stool and other concomitant pathology will be discussed further in Chapter 7.

A sizeable number (40,2 percent) of the patients received one or more antibiotics during their stay in the rehydration ward. Penicillin either alone or in combination was the most frequently prescribed antibiotic (Table 5.11). In most instances the indication for use was a presumed infection of the upper or lower respiratory tract. Systemic antibiotics were not used as specific treatment for diarrhoea in this study. Antibiotics appear to have no place in the treatment of most

cases of infantile diarrhoea[108] and their widespread use in certain areas gives cause for concern. In the majority of patients given antibiotics in this study a review of their subsequent course suggested that the outcome was not materially altered by the use of an antibiotic. The use of antibiotics in sick infants in whom there is a possibility of bacterial sepsis is understandable but this study indicates that in fact the incidence of significant sepsis is low.

A specific treatment for persistent diarrhoea consisting of an oral combination or "cocktail" of Gentamycin, Metronidazole and Cholestryamine was used in a few instances. This form of treatment has been shown to be effective in stopping diarrhoea in many infants with persistent diarrhoea of 5 to 7 days duration[20,62]. It is used frequently for this purpose at the Children's Hospital but is not recommended for outpatient or home use. Since the "cocktail" is not initial therapy it is mostly prescribed once children have been transferred to the hospital wards for further management.

The rehydration ward at the Children's Hospital aims to rehydrate infants and children with dehydrating diarrhoea and discharge them home as soon as hydration is maintained on oral feeds. The children are discharged despite the fact that in many the stools are still abnormal. The results of this study confirm the short-stay status of the rehydration ward as 65,4 percent of infants had been discharged within 2 days and a further 16,8 percent within 3 days. Longer stay patients occurred in periods of high incidence (i.e. summer months) when the pressure on hospital beds was such that earlier transfer from the rehydration ward was not possible. In a previous study of admissions to the rehydration ward undertaken at the Children's Hospital[19] most had

been discharged within 3 to 4 days. Abraham et al[1] in a study of infantile diarrhoea found that 12 percent required intravenous therapy for 3 days compared to 17,8 percent in the current study. In the majority of infants the disease is acute, self-limiting and amenable to short term management in a rehydration ward. In a small number persistent or chronic diarrhoea results. In the current study 17,4 percent required transfer to a hospital ward which is higher than the 9,5 percent reported by Bowie in 1960[19]. This difference probably reflects greater availability of hospital beds rather than increased severity of disease in the recent study. Once hospitalised most infants remained there for at least 10 days with the hospital stay ranging from less than 5 to over 30 days (Figure 5.13).

Mortality was extremely low with only one death in the rehydration ward and 7 further deaths reported subsequent to discharge giving an overall 1,5 percent mortality rate. This may be a slight underestimation but it is significantly better than the 9,5 percent mortality reported by Bowie[19]. Abraham et al[1] in their study from Egypt report a 5 percent death rate. In other areas the mortality for children hospitalised with diarrhoea is considerably higher. In Jakarta the mortality over a 3 year period ranged from 14 to 22 percent[118]. Nazer[108] in his review reports that high mortality rates ranging up to 20 percent are associated with diarrhoeal disease in the developing world. Datta Banik[36] found a 5-6.5 percent mortality in a study of preschool children from India while a report from Jordan[78] showed a 5 percent mortality. In developed countries mortality rates are of the order of 1 percent[108]. The results reported leave little doubt that adequate and early oral or intravenous rehydration can significantly reduce the mortaility but in many areas this is not available. Field

trials in Guatemala, India and Indonesia showed high attack rates of 1 to 2 episodes of diarrhoea per child per year making adequate provision of hospital facilities almost impossible in underdeveloped areas[118]. For this reason programs to initiate early oral rehydration with glucose and electrolyte solutions have been promoted worldwide by the World Health Organisation (WHO) and others as an alternative form of management.

Fifteen percent of the infants studied were readmitted to the rehydration ward within the 6 month review period following discharge. Since dehydration requiring intravenous rehydration is an indication of severe diarrhoea the actual recurrence rate of diarrhoea was probably much higher. Rohde and Northrup[118] estimated the case rate of Asia, Africa and Latin America at 100 episodes/100 children per year in the first year of life, increasing to a maximum of 140 episodes/100 children per year from 1 to 2 years of age. These include all episodes of diarrhoea while infants in the current study only reflect the severe cases. No estimate of the attack rate can be made from the current study but in view of relapse rate of severe diarrhoea it can be presumed to be high.

CONCLUSIONS

The results in this chapter reflect the general characteristics of the infants studied. As a random sample of the larger group admitted to the rehydration ward they reflect the characteristics of the latter. To a lesser extent the characteristics of the Black and Coloured infants in the greater Cape Town area are also reflected.

The infants studied were relatively well nourished and in 75 percent there was no previous history of diarrhoea. This lends support to the hypothesis that diarrhoeal disease is an important precipitating factor of malnutrition in infants and children. The relationship between diarrhoea and malnutrition is discussed in relation to the findings of this and other studies.

The high incidence of hypoalbuminaemia in the current study probably secondary to large protein losses in the stools is indictive of the severe nutritional insult caused by acute diarrhoeal disease. In most infants the diarrhoea was of short duration ($<$3 days). Some developed more persistent diarrhoea (16 percent) requiring hospitalisation for more than 10 days. Others (15 percent) had a recurrence of sufficient severity to warrant readmission to the rehydration ward. These infants with persistent or recurrent diarrhoea are those particularly at risk for the development of malnutrition. Early effective treatment of acute diarrhoeal episodes aimed at the prevention of persistent diarrhoea is a priority in those infant populations with a high prevalence of diarrhoeal disease. Reduction of the recurrence rate and the attack rate (the latter not determined in this study) may similarly reduce the incidence of malnutrition seen often at a later age in these population groups.

This study confirms the nonspecific clinical picture of acute infantile diarrhoeal disease. Inaccuracies in the clinical assessment of the degree of dehydration and metabolic acidosis are highlighted. Problems related to the diagnosis of middle ear disease and its clinical importance are discussed. In 9,4 percent other disease such as pneumonia, urinary tract infection or measles may have contributed as a

parenteral cause of the diarrhoea. Bacterial invasion was uncommon and blood cultures were positive in only 4,6 percent.

Serum electrolytes were disturbed in many of the patients. The findings are comparable with previous studies in the rehydration ward at the Children's Hospital. Hyponatraemia and hypokalaemia occurred most frequently. The haematological findings although abnormal in many did not contribute to the management in most cases. Possible iron deficiency indicated by a reduced MCV was present in 24 percent. Antibiotics were not routinely used for the treatment of diarrhoea. They were nevertheless frequently prescribed (40,2 percent) most often for respiratory tract infection.

The rehydration ward effectively rehydrated the majority of infants admitted. Eighty two percent were discharged home within 3 days. The death rate in the rehydration ward was 0,2 percent and overall, including late deaths, the death rate was 1,5 percent. These results are comparable with many reports from developed countries despite the lower socio-economic communities from which the infants originated.

CHAPTER 6

STOOL ENTEROPATHOGENS

Stool specimens from 545 infants with diarrhoea and 297 infants without diarrhoea were investigated according to the methods outlined in Chapter 3. The incidence of possible enteropathogenic microorganisms was established in patients and controls. The significance of a particular microorganism was determined by statistical comparison (X^2 test) of the incidence between the two groups).

RESULTS:

6.1. STOOL ISOLATES

Overall incidence of bacteria, rotavirus and intestinal parasites.

The monthly totals for patients and controls are shown in Table 6.1 and graphically in Figures 6.1A and 6.1B. The possible enteropathogens isolated from the stools of patients and controls are detailed in Tables 6.2 and 6.3 and graphically in Figure 6.2.

6.1.1. Rotavirus

Rotavirus was isolated in 18,1 percent of patients and 3,9 percent of controls tested. Due to insufficient collection of stool, or in a few, inadequate storage 52 stool specimens in the

Figure 6.1A MONTHLY PATIENT TOTALS

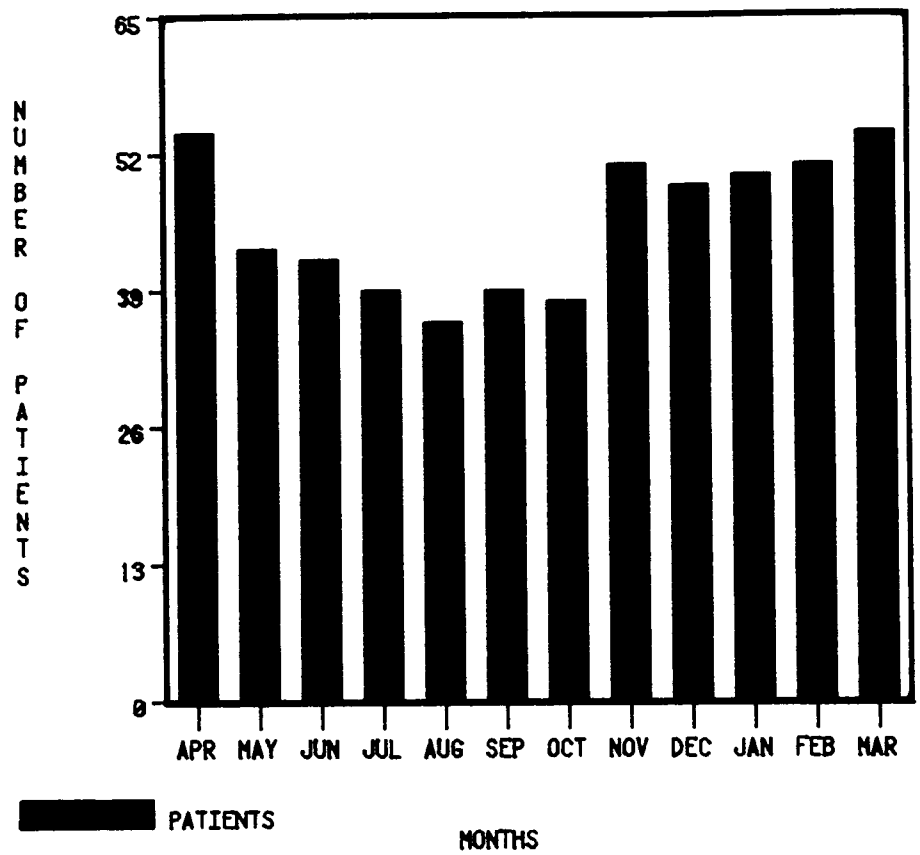


Figure 6.1B MONTHLY CONTROL TOTALS

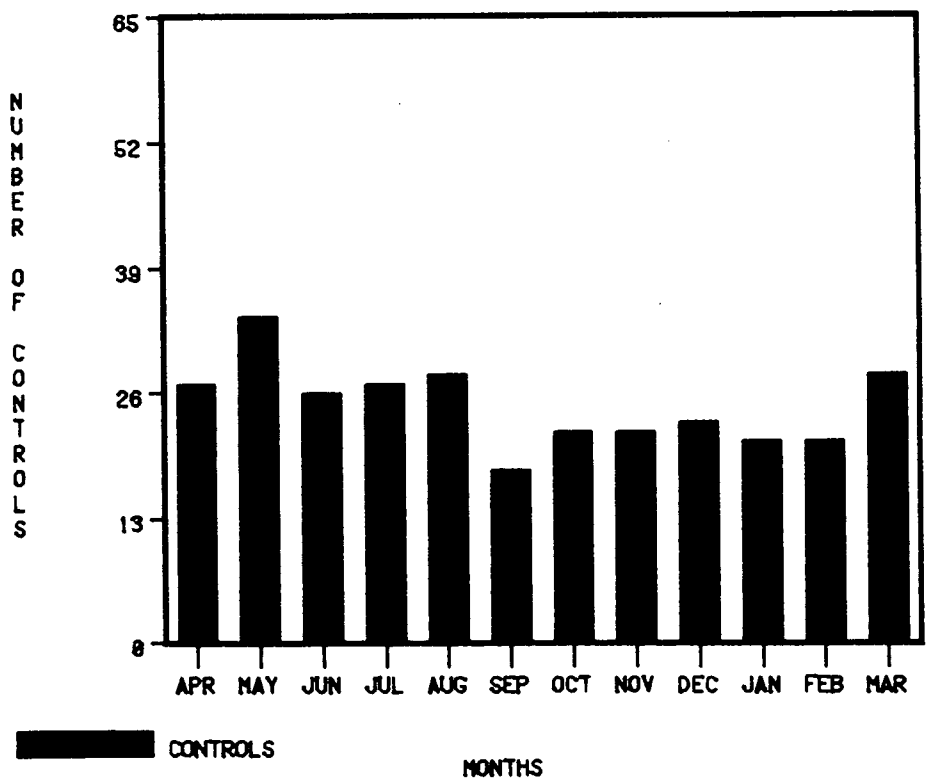


Figure 6.2 GROUPS OF PATHOGENS

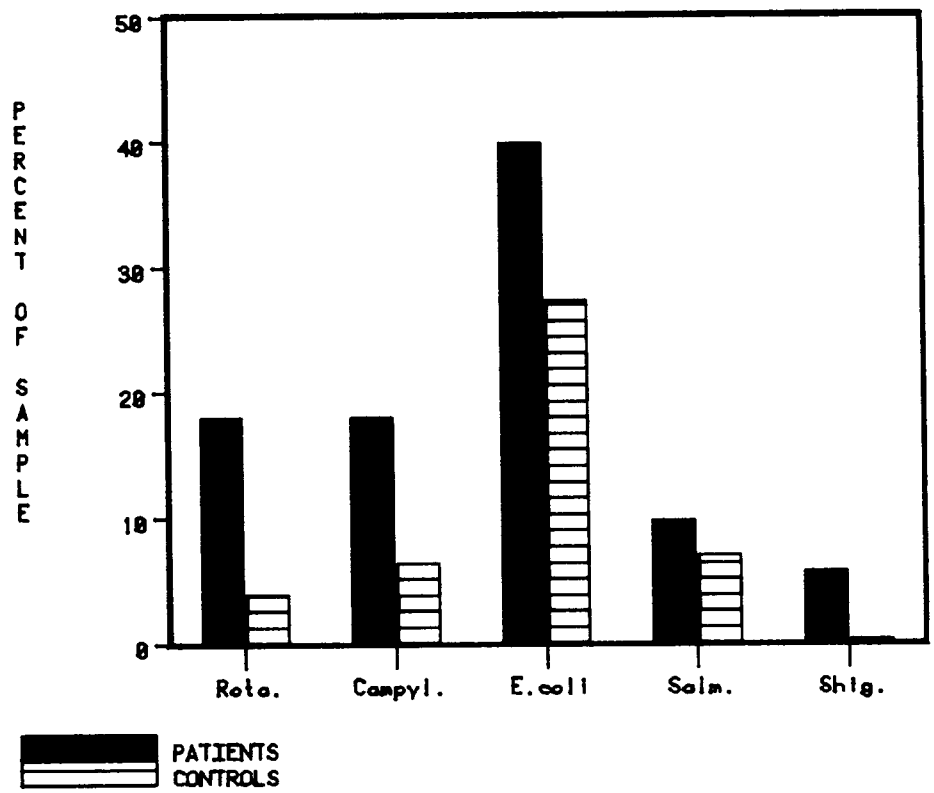


TABLE 6.1

MONTHLY STUDY TOTALS

	PATIENTS		CONTROLS	
	*ALL SPECIMENS	+ROTAVIRUS ELISA	ALL SPECIMENS	ROTAVIRUS+ ELISA
APR	54	52	27	27
MAY	43	38	34	33
JUN	42	34	26	21
JUL	39	38	27	27
AUG	36	32	28	27
SEP	39	37	18	18
OCT	38	34	22	19
NOV	51	46	22	22
DEC	49	43	23	22
JAN	50	48	21	21
FEB	51	41	21	14
MAR	54	50	28	28
YEAR TOTALS	545	493	297	279

* Indicates all specimens received

\+ Indicates those tested by Rotazyme ELISA technique

TABLE 6.2

STOOL ISOLATES (ALL ORGANISMS)

	PATIENTS		CONTROLS		
	n = 493	percent	n = 279	percent	
Rotavirus	89	18,1	11	3,9	*p < 0,0001
	n = 545	percent	n = 297	percent	
Campylobacter fetus jejuni	98	18	19	6,4	*p < 0,0001
Shigella A	1	0,2	0	0	
B	15	2,7	0	0	*p < 0,01
C	2	0,4	0	0	
D	13	2,4	1	0,3	*p < 0,05
All types	31	5,7	1	0,3	*p < 0,0005
Salmonella B	29	5,32	4	1,35	*p < 0,01
C1	9	1,65	2	0,67	NS
C2	11	2,01	6	2,02	NS
D	2	0,37	2	0,67	NS
E	1	0,18	5	1,68	NS
F	1	0,18	0	0	NS
G	3	0,55	0	0	NS
K	1	0,18	0	0	NS
N	1	0,18	0	0	NS
R	1	0,18	2	0,67	NS
All types	59	10,8	21	7,06	*p = 0,1
Yersinia enterocolitica	5	0,9	0	0	NS

* (X^2 test)

NS = not significant

patient group and 18 in the control group were not tested for rotavirus. There was a strong statistical association with the presence of diarrhoea when the incidence was compared with the controls (X^2 test $p < 0,0001$)

6.1.2. Campylobacter fetus ss jejuni

Campylobacter fetus occurred in 18 percent of patients and 6,4 percent of controls. Its presence was statistically associated with the presence of diarrhoea (X^2 test $p < 0,0001$),

6.1.3. Shigella

Shigella (Figure 6.3) of all types was more frequently isolated in infants with diarrhoea. The overall incidence was 5,7 percent as opposed to 0,3 percent in the controls ($p < 0,0005$). On statistical analysis only types B and D achieved significant levels ($p < 0,01$ and $< 0,05$ respectively) although types A and C occurred only in infants with diarrhoea.

6.1.4. Salmonella

Salmonella (Figure 6.4) occurred relatively frequently in both patients (10,8 percent) and controls (7,06 percent) but only Salmonella group B was significantly associated with the presence of diarrhoea ($p < 0,01$).

Figure 6.3 SHIGELLA

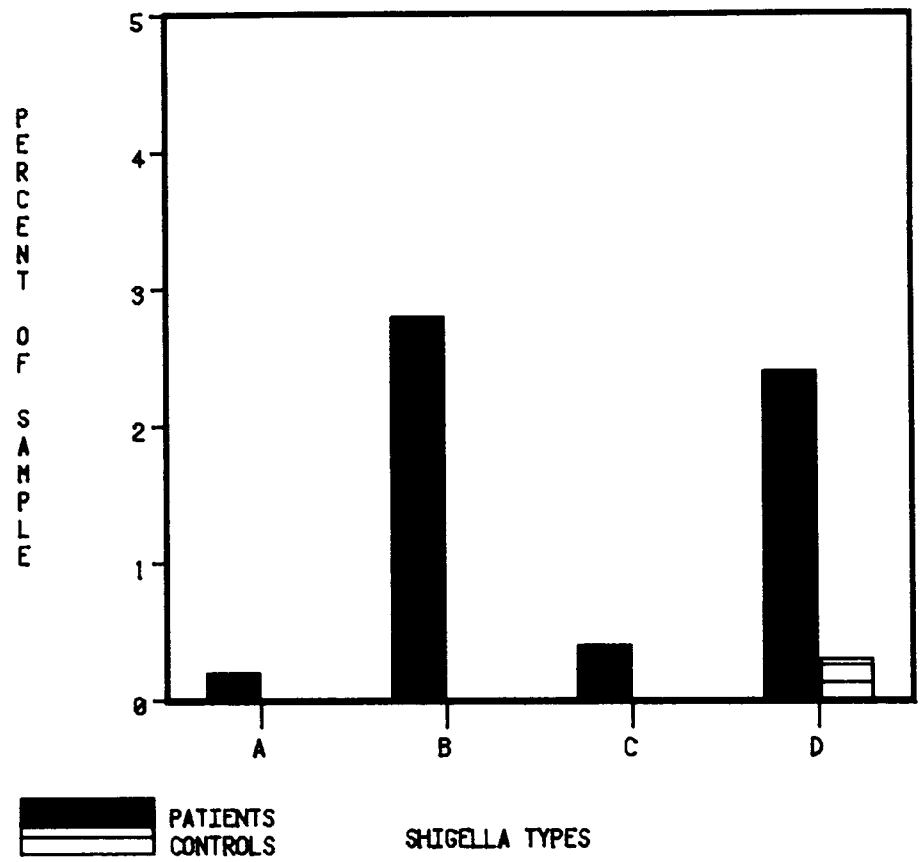
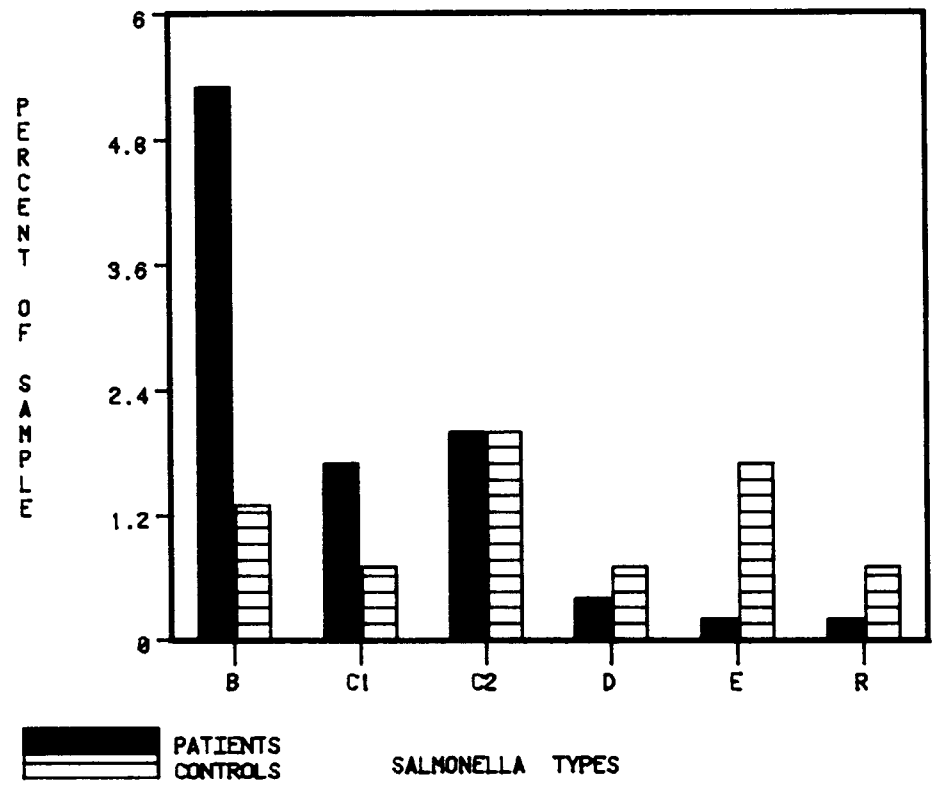


Figure 6.4 SALMONELLA



6.1.5. Yersinia enterocolitica

Yersinia enterocolitica was isolated in 5 patients and not in the control group. While this was suggestive of an association with diarrhoea siginificant levels were not achieved on statistical analysis due to the small number.

6.1.6. Enteropathogenic Escherichia coli

The detailed results for the enteropathogenic Escherichia coli (EPEC) identified by grouping sera are given in Table 6.3. Of the 15 enteropathogenic types potentially identifiable, 14 were isolated in the patient group and 13 in the controls. Although a commonly isolated gram negative bacteria, only three types showed a significant association with the presence of diarrhoea: (Figure 6.5) EPEC strains 0126:K71(B16) $p < 0,001$; 0119:K69(B14) $p < 0,05$ and 0127:K63(B8) $p < 0,05$. Other strains notably 055:K59(B5); 086:K61(B7); 011:K58(B4) and 0114:K90(B) were more common in the patients with diarrhoea but did not achieve statistical significance. One EPEC strain 044:K74(L) had a reversed association with the presence of diarrhoea ($p < 0,01$) while a further strain 018c:K77 (b21) occurred frequently in both patients (7,9 percent) and controls (9,4 percent) with no statistical difference between the two groups.

6.1.7. Intestinal parasites

Intestinal parasites were very uncommon. Only Giardia lamblia was identified and this in 2 patients compared to 7 controls.

TABLE 6.3

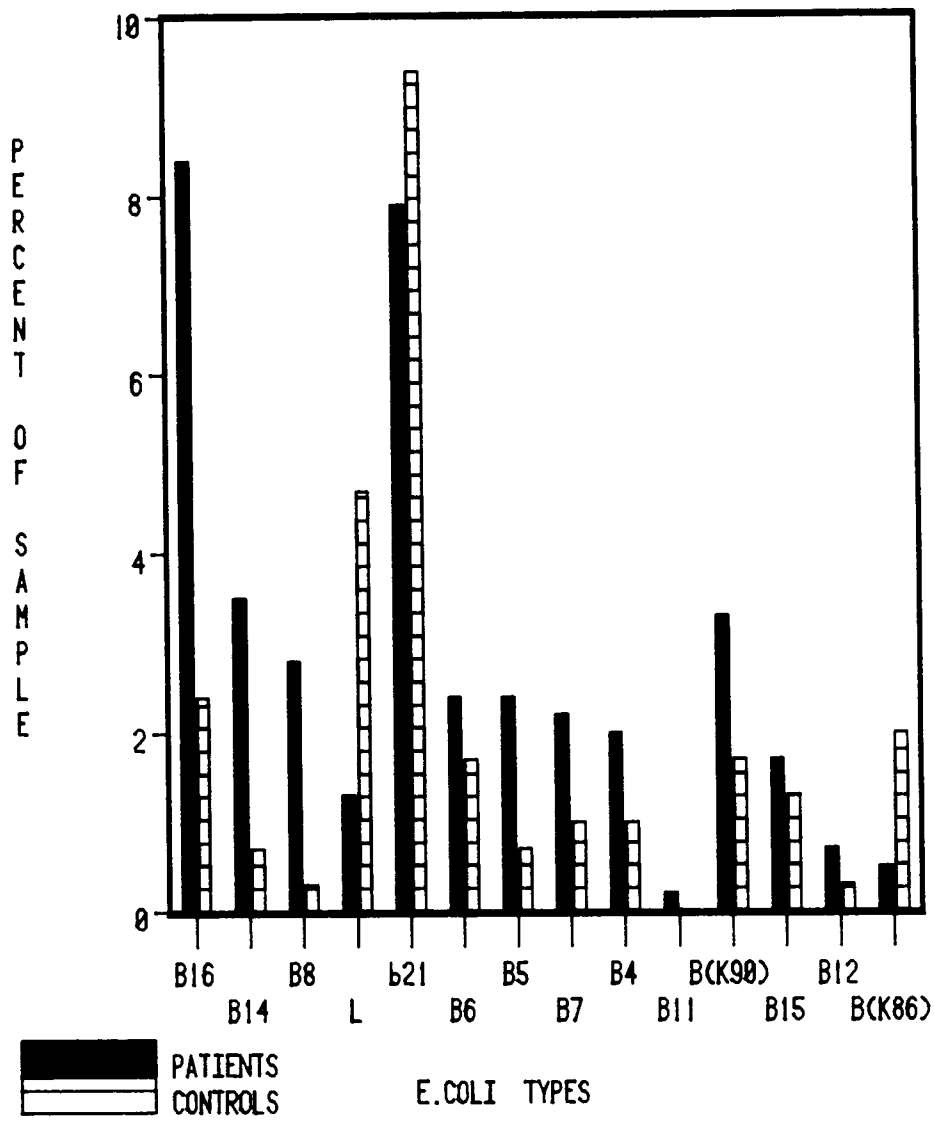
ENTEROPATHOGENIC ESCHERICHIA COLI STOOL ISOLATES

	PATIENTS		CONTROLS		
SEROTYPE	(n = 545)	Percent	(n = 297)	Percent	
0126:K71 (B16)	46	8,44	7	2,36	$^{*}p < 0,001$
0119:K69 (B14)	19	3,48	2	0,67	$^{*}p < 0,05$
0127:K63 (B8)	15	2,75	1	0,34	$^{*}p < 0,05$
044:K74 (L)	7	1,28	14	4,71	$^{*}p < 0,01$ (reversed)
018c:K77 (b21)	43	7,89	28	9,43	NS
026:K60 (B6)	13	2,39	5	1,68	NS
055:K59 (B5)	13	2,39	2	0,67	NS
086:K61 (B7)	12	2,20	3	1,01	NS
0111:K58 (B4)	11	2,01	3	1,01	NS
0112:K66 (B11)	1	0,18	0	0	NS
0114:K90 (B)	18	3,30	5	1,68	NS
0125:K70 (B18)	9	1,65	4	1,35	NS
0128:K67 (B12)	4	0,73	1	0,34	NS
0142:K86 (B)	8	1,47	6	2,02	NS
TOTAL EPEC TYPES 1	219	40,18	81	27,27	NS

* (X^2 test)

NS = Not Significant

Figure 6.5 ENTEROPATHOGENIC E.COLI



6.2. MONTHLY VARIATION IN THE DETECTION RATES OF POSITIVE STOOL ISOLATES

Analysis of stool isolates to determine the monthly detection rate of the respective micro-organisms in the study sample reveals certain trends. Rotavirus (Figure 6.6) and Campylobacter (Figure 6.7) in the patient group show a somewhat similar monthly variation over the 12 month study period. The peak for rotavirus is in August (28,1 percent of stools examined had rotavirus) and March (24 percent). A period of higher incidence occurs from February to August ($p < 0,01$) and this corresponds to late summer, through autumn to winter. Low detection rates for rotavirus occur in the patient group from September to January with the nadir in December (9,3 percent). This corresponds with early spring to midsummer. The occurrence of rotavirus in the control group is paradoxically highest in October (10,5 percent) and December (9,1 percent), periods of low occurrence in the patient group.

Campylobacter was characterised by a period of greater prevalence during the months May to August with a peak in June (28,6 percent). During this period Campylobacter was found significantly more frequently than during the rest of the year ($p < 0,0005$). The lowest prevalence in the patient group was during November (7,8 percent) but overall the period of lower prevalence was not as marked as with rotavirus. Campylobacter was most often present in the controls during periods of high occurrence in the patient group. The highest isolation rate of 23,8 percent in the control group occurred in February when the

Figure 6.6A ROTAVIRUS PATIENTS MONTHLY

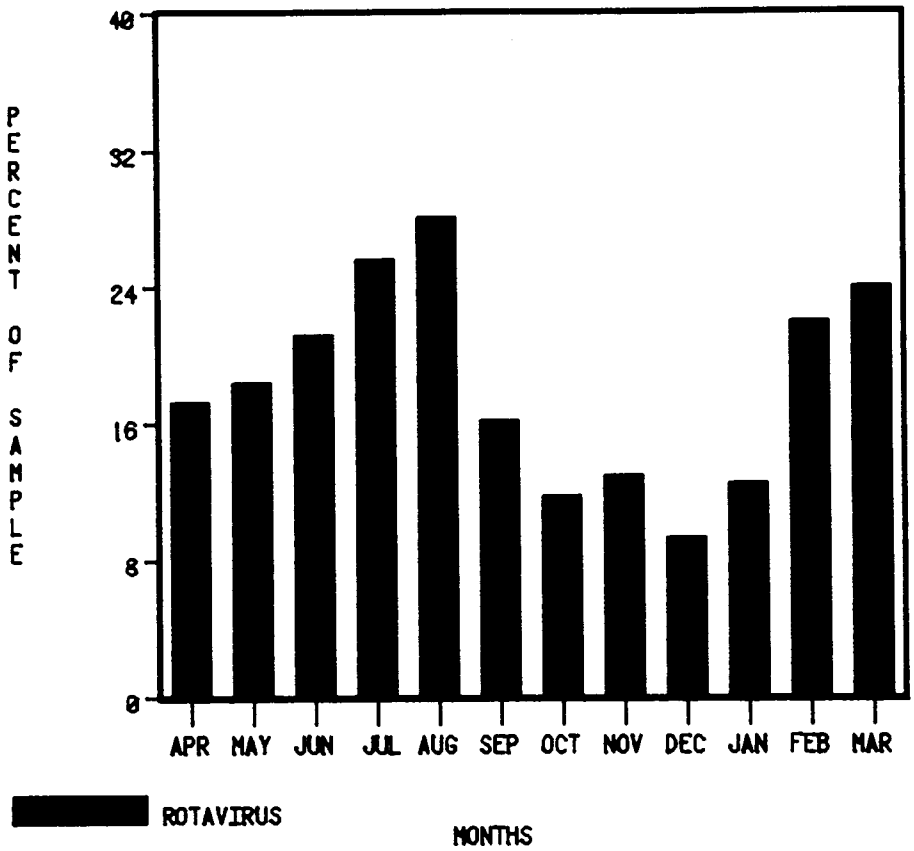


Figure 6.6B ROTAVIRUS CONTROLS MONTHLY

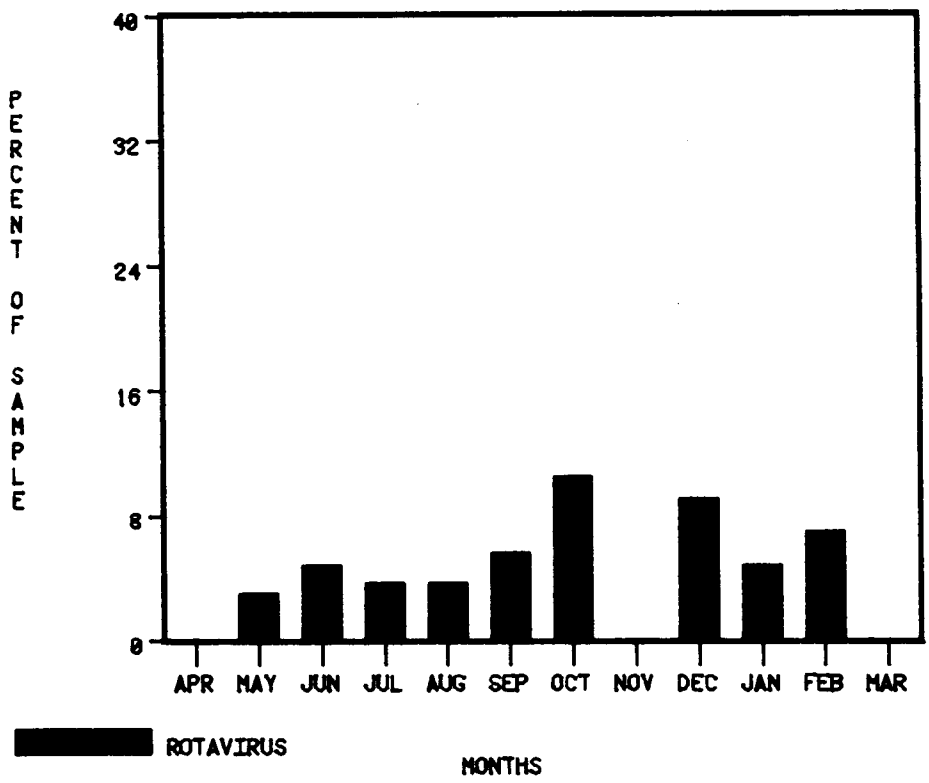


Figure 6.7A CAMPYLOBACTER PATIENTS MONTHLY

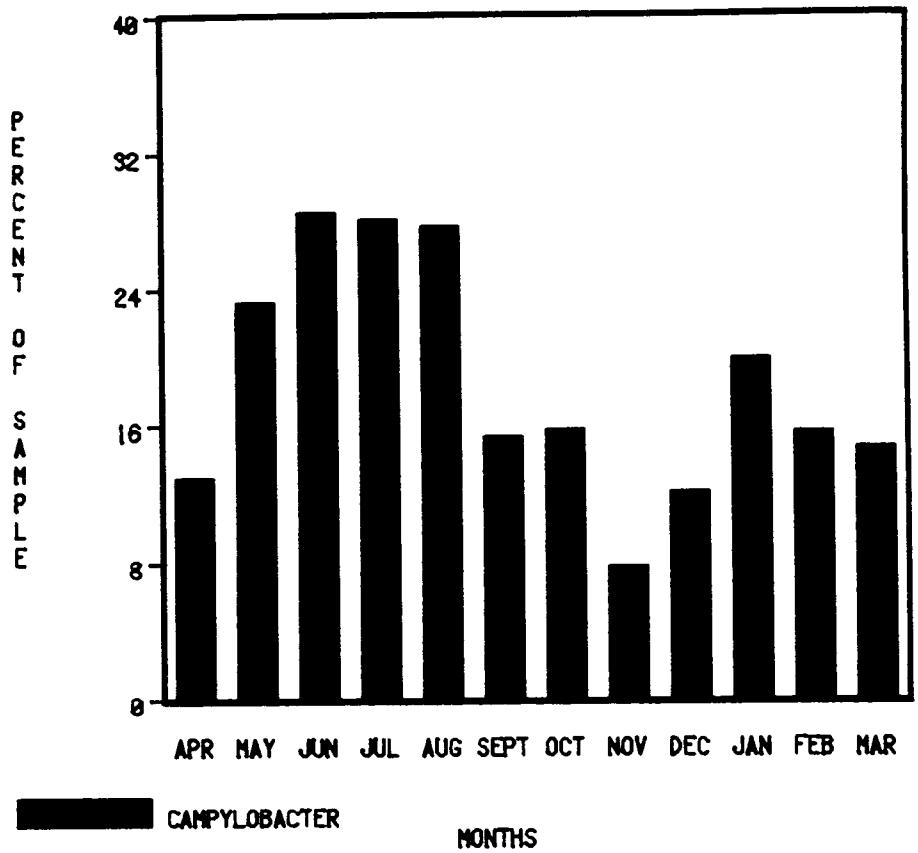
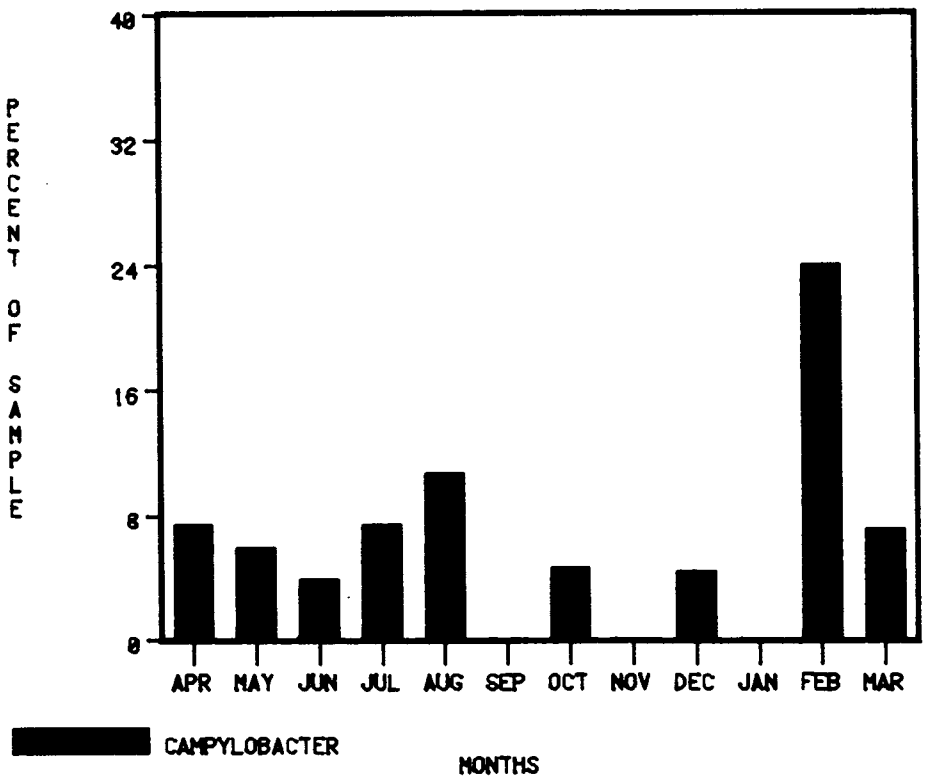


Figure 6.7B CAMPYLOBACTER CONTROLS MONTHLY



incidence in the patients was 15,7 percent.

Shigella of all four types (Figure 6.8) was virtually exclusive to the patient group and occurred with low frequency throughout the year. The highest detection rate in January (10 percent) and the lowest in September (2,6 percent). Only one Shigella was cultured in the controls and this in the first month of the study. Salmonella (Figure 6.9A) occurred more frequently than Shigella and was present throughout the year in the patient group. The highest incidence was recorded in August (19,4 percent) when as in September and April it was isolated relatively frequently in the patients but not in the controls. A monthly analysis of all isolates of Salmonella excluding Salmonella group B (shown previously to have an overall statistical association with the presence of diarrhoea) suggests that during certain periods Salmonella other than group B may be significantly associated with diarrhoea. This trend was evident in April, August and February when no Salmonella were isolated in controls but did not achieve statistical significance (Figure 6.9B).

Enteropathogenic E.coli were the most frequently isolated bacteria in the stools of both patients and controls (Figure 6.10). A peak occurred in May (60,5 percent) and September (53,9 percent) in the patients and this was mirrored in the controls. Periods of low isolation rates of EPEC were June, July and November while in the controls the corresponding months were June to August and October.

Figure 6.8 SHIGELLA MONTHLY ANALYSIS

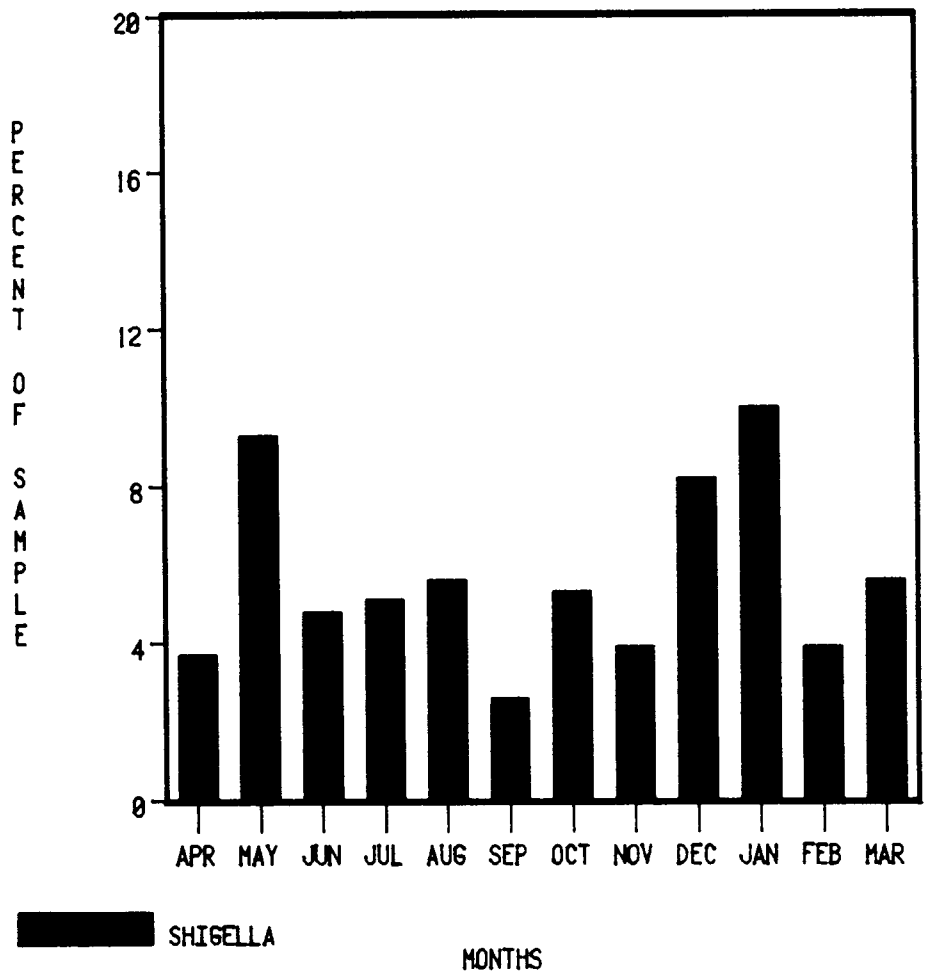


Figure 6.9A SALMONELLA MONTHLY ANALYSIS

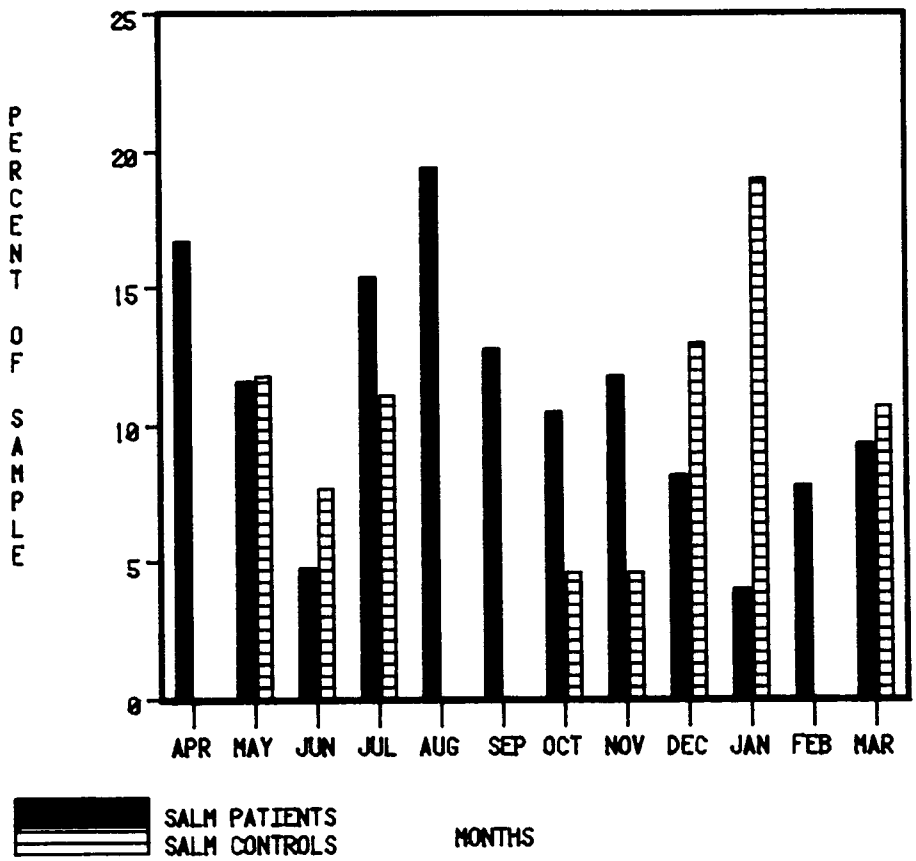


Figure 6.9B SALMONELLA MONTHLY ANALYSIS (Type B vs All types)

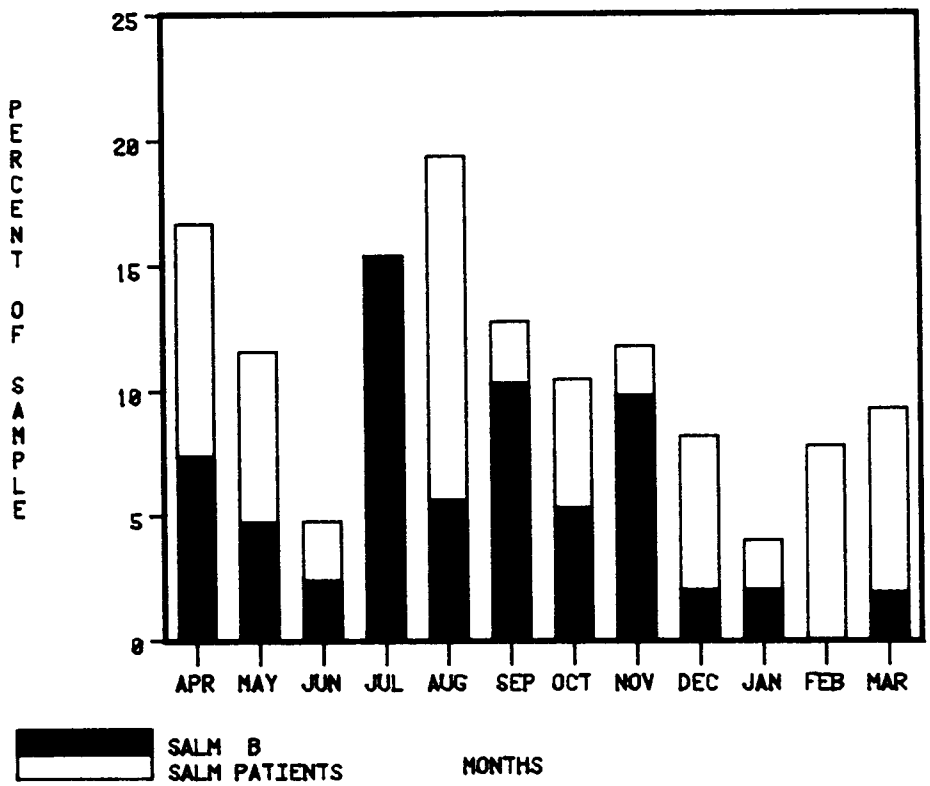
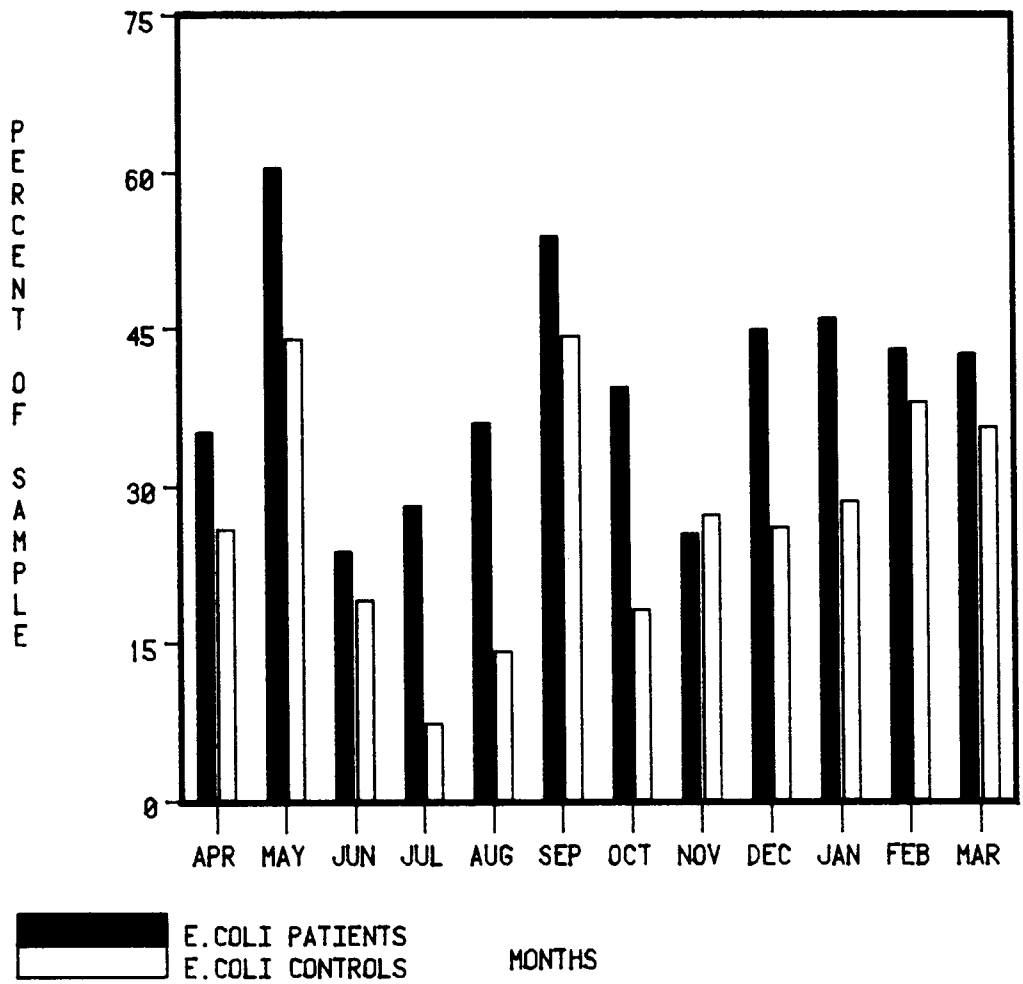


FIGURE 6.10 EPEC MONTHLY TOTALS



EPEC type 0126:171(B16) was significantly assoicated with diarrhoea taken overall ($p < 0,001$). However, if the months May to July are analysed separately there is no significant difference between patients and controls. Analysis (X^2 test) for the rest of the year shows a statistically significant association between the isolation of EPEC 0126:K71(B16) and the occurrence of diarrhoea ($p < 0,0005$). A graph showing the comparative monthly detection rates of all possible enteropathogens isolated in the stools is shown in Figure 6.11A. Figure 6.11B demonstrates the monthly detection rates of those enteropathogens shown to be statistically significant. This graph illustrates that if only the EPEC types found to be significant are included, the relative significance of EPEC is reduced. In addition the frequency of positive isolates is more evenly spread throughout the year. Only in December and January are significant EPEC types the numerically dominant pathogens isolated.

Weekly analysis of the data is complicated by the small sample size in some weeks resulting in spuriously high incidence of certain organisms. Weekly analysis did not reveal any trends not demonstrated by the monthly figures and for this reason has not been presented separately.

6.3. SEASONAL VARIATION OF PATIENTS WITH POSITIVE STOOL ISOLATES

A monthly analysis of patients and controls with positive stool isolates including all organisms isolated is shown in Figure 6.12A. A similar analysis including only those isolates with

Figure 6.11A ALL STOOL ISOLATES MONTHLY

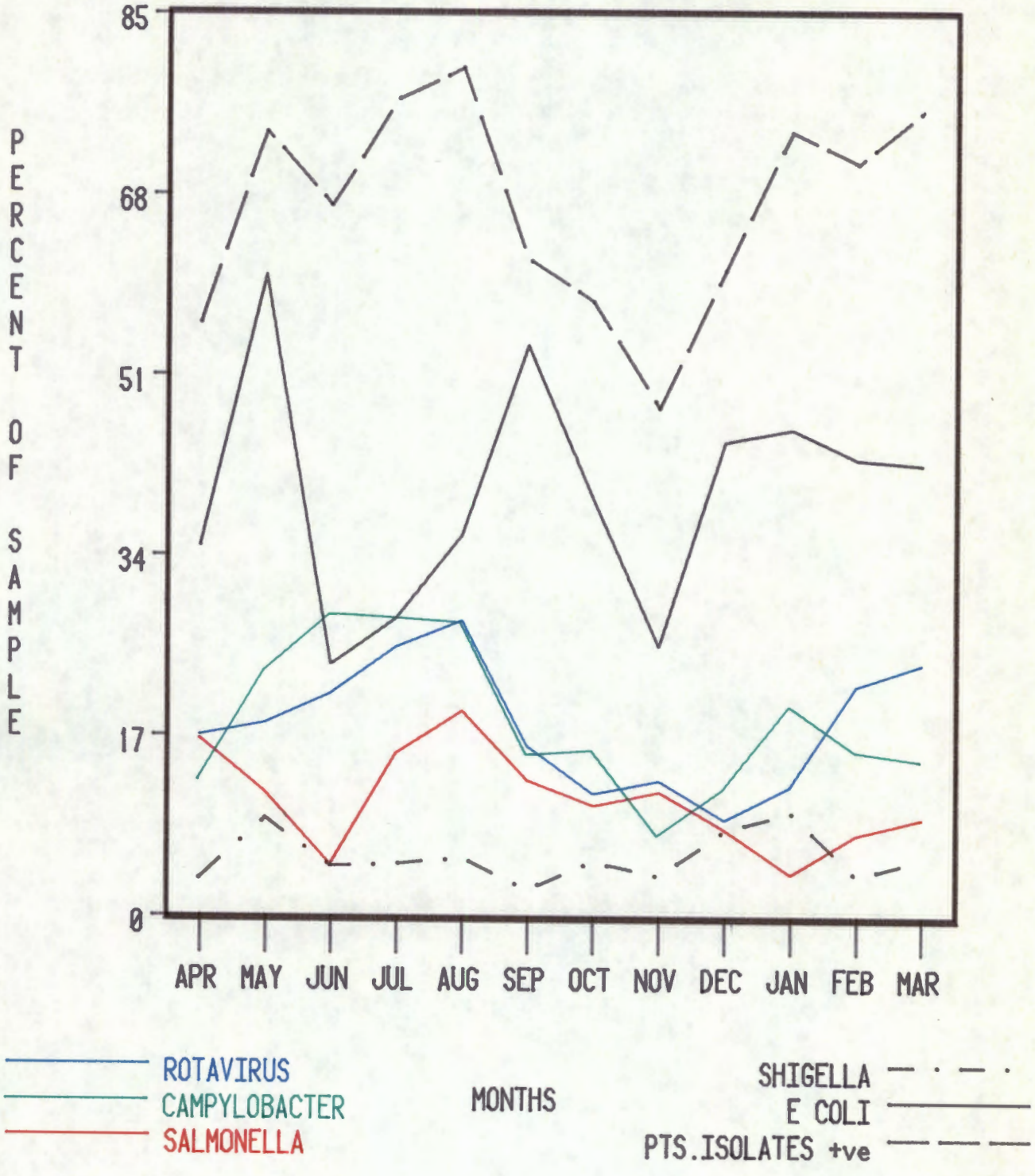
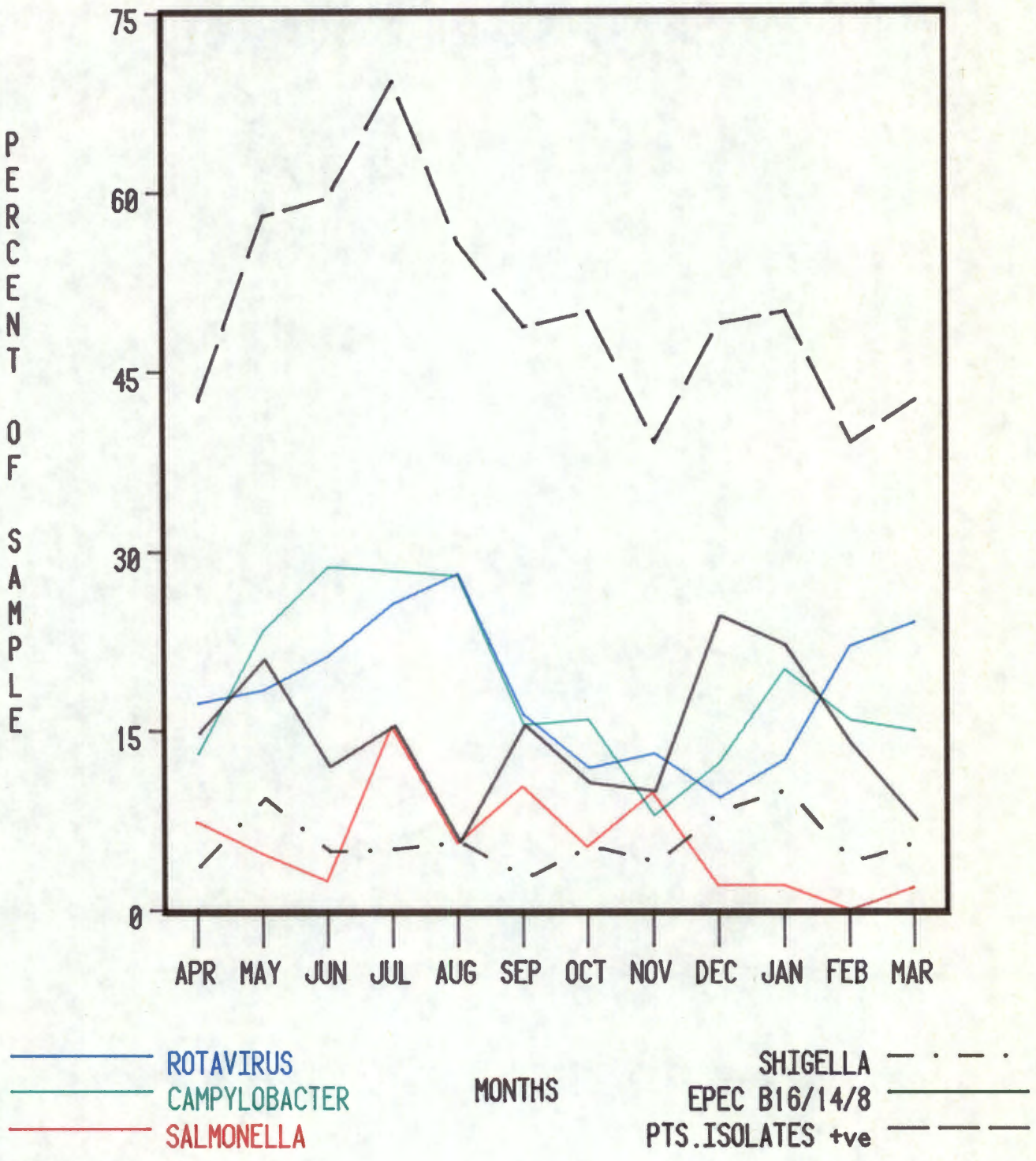


Figure 6.11B SIGNIFICANT STOOL ISOLATES MONTHLY



significant organisms is shown in Figure 6.12B. If all organisms isolated are taken into account the highest monthly incidence in the patient group occurs in August (80 percent). A prominent feature is the significant trough from September to November ($p < 0,005$) when the incidence of positive isolates falls to a low point of 49 percent in November. This corresponds to spring and early summer. The bulk of organisms isolated are EPEC but during July and August the high frequency of positive isolates is due to a combination of rotavirus, Campylobacter and Salmonella in addition to EPEC (Figure 6.11A).

When the significant organisms are analysed separately the picture in the patient group is different (Figure 6.11B). A period of high incidence occurs from May to August when predominant rotavirus and Campylobacter are isolated (Figure 6.12A). This differs significantly ($p < 0,0001$) from the rest of the year when values are relatively constant. May to August are the late autum and winter months. It is notable that EPEC are no longer the most frequent positive stool isolates if non-significant EPEC are excluded. They are in the majority only during December and January.

6.4 INCIDENCE OF SINGLE, MULTIPLE AND NON-SIGNIFICANT ISOLATES

A significant number of patients (126) and controls (18) had more than one organism isolated in the stool. To determine the total number of patients and controls with either no organisms or one or more organisms identified in the stool, an analysis of the combinations of enteropathogens isolated was necessary. The

Figure 6.12A PATIENTS with POSITIVE STOOL ISOLATES

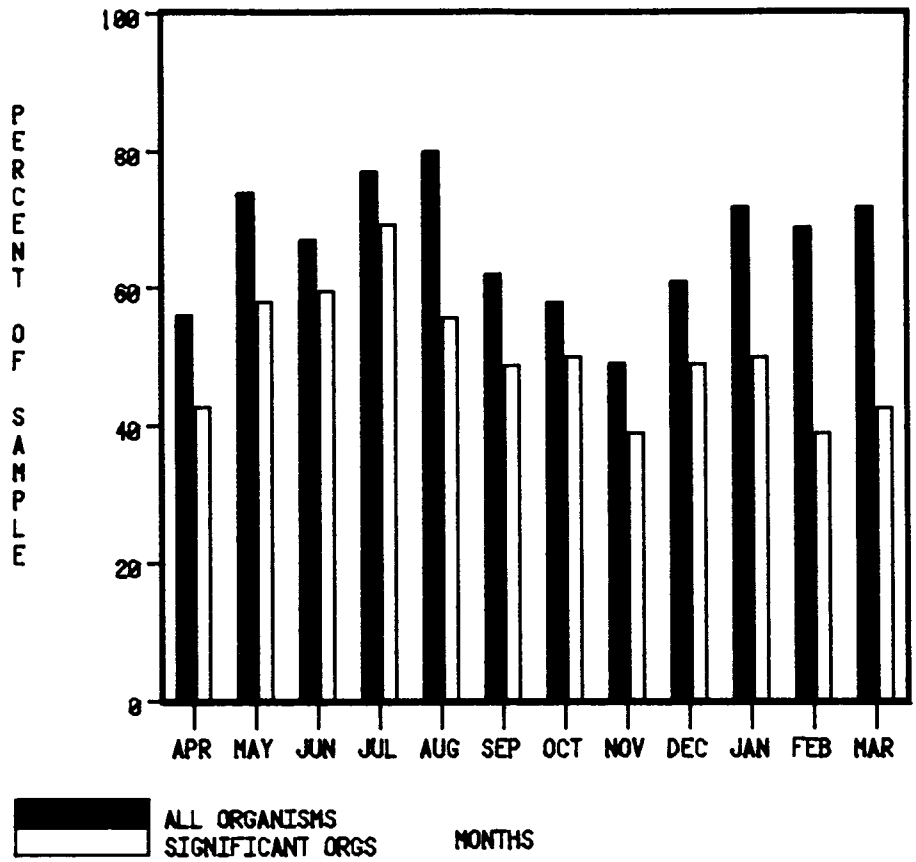
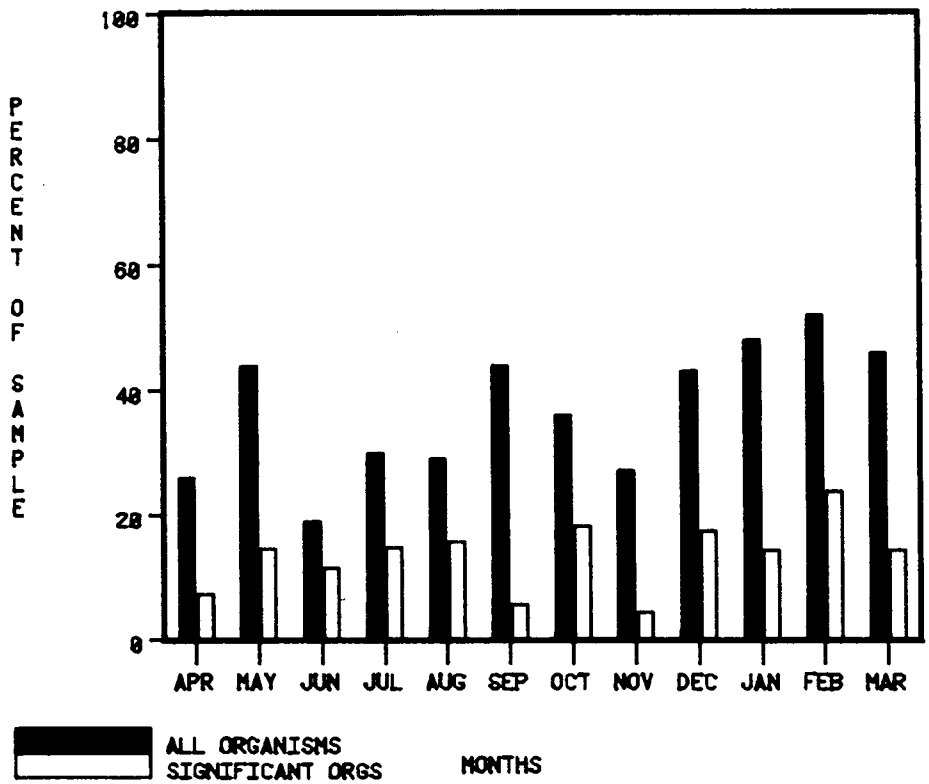


Figure 6.12B CONTROLS with POSITIVE STOOL ISOLATES



combinations present in both groups are shown in Tables 6.4. In the patient group when all the organisms isolated are included, a majority (360 or 66 percent) have one or more organisms in the stool. In the control group the majority have no organisms identified in the stool (188 or 63,2 percent).

If only those organisms considered likely to have an association with the presence of diarrhoea in this study are included, (i.e. rotavirus, Campylobacter fetus ss jejuni, EPEC types B16, B14, and B8, Salmonella group B, Shigella of all types and Yersinia enterocolitica) as outlined in Tables 6.2 and 6.3, the findings differ. One or more organisms are present in 49,4 percent of the patient group compared with 13,8 percent in the controls.

Multiple stool isolates (i.e. 2 or more organisms isolated per patient) were not uncommon. Twenty three percent of patients had multiple stool isolates of any enteropathogens while 10,1 percent had multiple isolates of those enteropathogens found to be significant in this study. This is graphically represented with corresponding values for the controls in Figures 6.13A and 6.13B. The decrease in multiple stool isolates when only significant organisms are considered results in an increase in the number of single isolates of rotavirus, Campylobacter and Shigella (Table 6.4).

Figure 6.13A ALL STOOL ISOLATES ORGANISMS/PATIENT

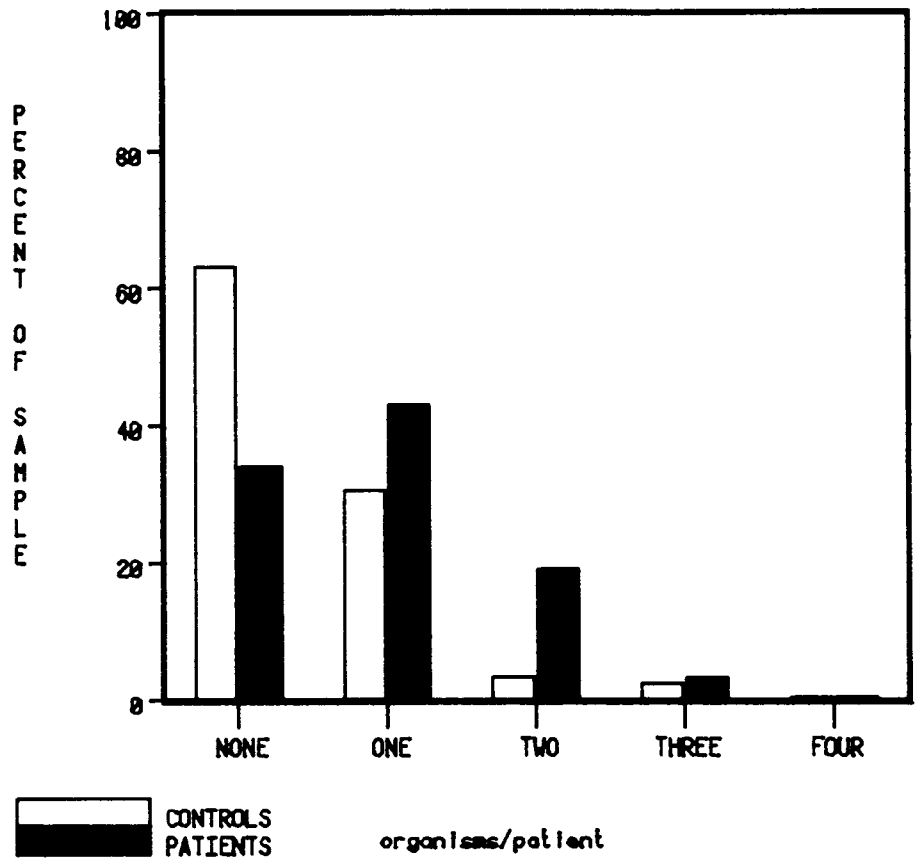


Figure 6.13B SIGNIFICANT STOOL ISOLATES ORGANISMS/PATIENT

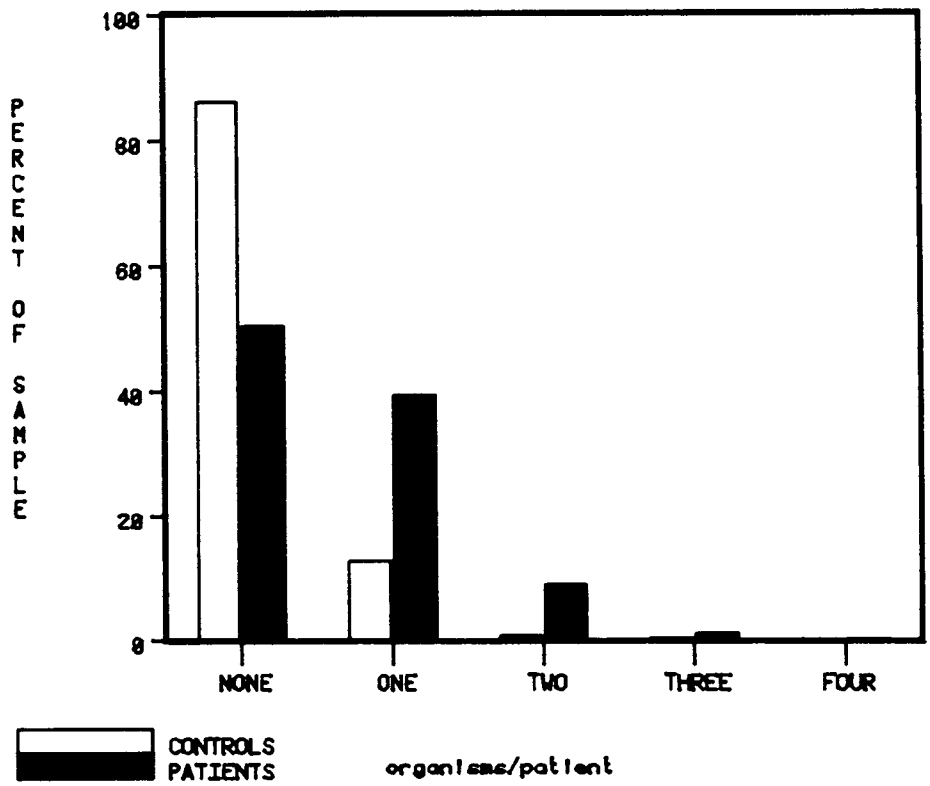


TABLE 6.4

STOOL ISOLATES (ORGANISMS PER PATIENT)

NO ORGANISMS ISOLATED

	PATIENT GROUP N = 545		CONTROL GROUP N = 297	
	[1]All isolates	*Significant isolates	[1]All isolates	*Significant
TOTAL (percentage)	185 (34%)	276 (50,6%)	188 (63,2%)	256 (86.2%)

ONE ORGANISM ISOLATED per PATIENT

ORGANISM	PATIENT GROUP N = 545		CONTROL GROUP N = 297	
	All isolates	Significant isolates	All isolates	Significant Isolates
ROTAVIRUS	41	58	7	9
CAMPYLOBACTER	40	60	13	16
E.P.E.C.	112	50	56	8
SALMONELLA	24	21	14	4
SHIGELLA	12	20	1	1
YERSINIA	5	5	0	0
TOTAL (Percentage)	234 (43%)	214 (39,3%)	91 (30,6%)	38 (12,8%)

[1] Includes ALL organisms identified in the stool specimens

* Includes only those organisms considered likely to be "significantly" associated with diarrhoea (see Tables 6.1 and 6.2): Rotavirus, Campylobacter Fetus jejuni, EPEC types B16, B14 and B8; Salmonella type B, Shigella types A to D and Yersinia enterocolitica.

Table 6.4: Stool Isolates (Organisms per patient) contd

TWO ORGANISMS ISOLATED PER PATIENT

ORGANISMS	PATIENT GROUP N = 545		CONTROL GROUP N = 297	
	[1] All	* Significant	All	Significant
Rotavirus + Campylobacter	10	11	0	1
Rotavirus + EPEC (1)	19	11	0	0
Rotavirus + Salmonella	6	1	1	0
Rotavirus + Shigella	2	2	0	0
Campylobacter + EPEC(1)	24	11	1	1
Campylobacter + Salmonella	7	4	0	0
Campylobacter + Shigella	4	6	0	0
Salmonella + EPEC(1)	18	3	5	0
Shigella + EPEC(1)	9	0	0	0
EPEC (2 types)	6	0	3	0
TOTAL (Percentage)	105 (19,2%)	49 (9%)	10 (3,4%)	2 (0,7%)

[1] Includes ALL organisms identified in the stool specimens

* Includes only those organisms considered likely to be "significantly" associated with diarrhoea (see Tables 6.1 and 6.2): Rotavirus, Campylobacter Fetus jejuni, EPEC types B16, B14 and B8; Salmonella type B, Shigella types A to D and Yersinia enterocolitica.

[2]MULTIPLE ORGANISMS

THREE ORGANISMS ISOLATED PER PATIENT

	All[1]	*Significant	All[1]	*Significant
TOTAL (Percentage)	18 (3,3%)	6 (1,1%)	7 (2,4%)	1 (0,3%)

FOUR ORGANISMS ISOLATED PER PATIENT

	All	Significant	All	Significant
TOTAL (percentage)	3 (0,5%)	0	1 (0,4%)	0

[2] Exact details in Annexure F.

[1] Includes ALL organisms identified in the stool specimens

* Includes only those organisms considered likely to be "significantly" associated with diarrhoea (see Tables 6.1 and 6.2): Rotavirus, Campylobacter Fetus jejuni, EPEC types B16, B14 and B8; Salmonella type B, Shigella types A to D and Yersinia enterocolitica.

DISCUSSION

The aetiology of infantile diarrhoea disease poses a complex multifactorial problem. In the many published surveys there remain a significant number of infants in whom no identifiable cause for the diarrhoea is found. Well designed controlled studies of infantile diarrhoeal disease, more especially from developing countries, are required. A survey to determine the enteropathogens associated with infantile diarrhoea at the Red Cross War Memorial Children's Hospital has not previously been undertaken. The results will be of value to those managing diarrhoea at this institution and indicate general trends in the community.

Viruses have long been suspected as enteropathogens but only with recognition of rotavirus by electronmicroscopy in the early 1970's has this been proved[66,154,171,182]. Initially identified as an important factor in childhood diarrhoea in developed countries, rotavirus has now been shown to be equally significant in developing areas[40,88,146,149]. The rotavirus attacks the small bowel and appears to have little or no effect on the stomach or colon. Animal studies indicate that the brush border of the mucosal cell is the primary target[47]. Duodenal biopsy material from infants has shown the virus within mucosal cells[14,171]. Levels of disaccharidase enzymes are depressed and xylose absorption is abnormal during rotavirus diarrhoea. Reliable identification by the ELISA[165,166] (Enzyme-linked immunosorbent Assay) technique has enabled less sophisticated laboratories in developing countries to identify rotavirus in the stool[26,66]. Other viruses may also be important in the pathogenesis of diarrhoea[66], but apart from the "non-cultivatable adenoviruses" none as yet appear of great significance in

children[14,50,58,152].

Bacteria such as Salmonella and Shigella have a well established role in the etiology of infantile dirrhoea. Salmonella penetrates the mucosa of the small and large intestine producing inflammation and mucosal damage[43,187]. Shigella acts both on the proximal small bowel producing a secretory diarrhoea and on the colon by invasion of the mucosa with consequent inflammation and acute bacterial colitis[43,77]. The role of Shigella toxins is as yet undefined in the pathogenesis of Shigellosis[77].

"Classic" enteropathogenic Escherichia coli (EPEC) of specific serotypes have been incriminated as enteropathogens in nursery and other defined outbreaks of infantile diarrhoea[43,120]. While their role has been questioned in the aetiology of infantile diarrhoea[38,52], there is work to suggest that in certain situations individual serotypes produce diarrhoea by an as yet undefined mechanism[44,55,79,86,89,148]. Escherichia coli have in addition, been shown to produce diarrhoea by other mechanisms. Enterotoxigenic E. coli produce heat-labile (LT) and heat-stable (ST) toxin that causes secretory diarrhoea[54,120]. Enteroinvasive E.coli (EIEC) able to adhere to and invade the small bowel mucosa produce diarrhoea but this mechanism appears less important in very young children[120]. In view of the large numbers in this study it was not possible to assess toxin production and enterovasion.

Recently Campylobacter fetus ss. jejuni has been identified as an important cause of childhood diarrhoea[15,16,109,136]. This microaerophilic vibrio invades the mucosa, but the mechanism by which it

causes diarrhoea has not been clearly defined[15]. It affects the jejunum, ileum and colon producing a bloody, exudative enteritis in some cases[172].

Yersinia enterocolitica has been shown to produce diarrhoea in children although it is a relatively infrequent cause. It also acts by an enteroinvasive mechanism[8,90]. Vibrio cholerae causes diarrhoeal disease in children in endemic or epidemic areas (notably India and elsewhere in the Far East) but it is not a major enteropathogen in the young infant even in these areas[40,85,88,144]. Food poisoning due to Staphylococcal enterotoxin is similarly not a significant cause of infantile diarrhoea[43].

Intestinal parasites such as Giardia lamblia and Trichuris trichuria are not important in the very young infant with diarrhoea, but assume greater significance in the older child. In endemic areas or when there has been travel to such areas, Entamoeba histolytica should always be considered as a cause of diarrhoea or dysentery in children.

Cryptosporidium a protozoan parasite has been identified recently as a cause of acute childhood diarrhoea. It appears unusual in infants under a year of age[100,162]. Prevalence has been reported at around 4 percent in the paediatric studies to date[67,101]. Cryptosporidiosis is a zoonosis but human to human transmission appears to be an important route of spread[107]. It is a cause of summer diarrhoea[100,162] and infection may be associated with other gastrointestinal pathogens most notably Giardia lamblia[161].

Clinical manifestations are a profuse watery diarrhoea with associated low grade fever, anorexia and abdominal pain in some cases. Diagnosis is confirmed by acid fast staining of the organism in stool specimens[35]. There is no specific treatment and management is supportive. Stools were not tested for Cryptosporidium in the present study as its possible relevance had not been recognized at the commencement of the study.

A review of more recent developments regarding the aetiological agents of acute infantile infectious diarrhoea is included in the Addendum.

Rotavirus

Rotavirus was found to be a significant cause of diarrhoea at the Children's Hospital with an 18,1 percent incidence in infants with diarrhoea (3,7 per cent in controls). No previous survey of the incidence of rotavirus has been done in Cape Town. The highest isolation rate for the patient group was 28,1 percent in August. Overall the incidence of rotavirus was less than that reported in many published African studies which varies from 4 to 61 percent [48,116,131,146,149]. Some of these reported only on periods of high prevalence of diarrhoeal disease. The current study was over a full year and the overall results are not comparable with these limited studies. The infants were either of mixed 'coloured' race or negroid origin. In a South African study by Freiman et al[48] approximately 14 percent of black infants seen at the Baragwanath Hospital with diarrhoea had rotavirus identified by electron microscopy. Shintzing et al[146] report on 27,8 percent incidence in 962 Ethiopian infants under one year of age in a year long study (8 percent in controls). Incidence in Asia

varies from 17 to 63 percent[14,39,40,80,87,88,136] but a study in India for one year comparable with the current study found a 26 percent incidence of rotavirus[88]. European and British surveys [23,87,121,152,157] report from 28 to 49 percent incidence using electron microscopy almost exclusively for diagnosis, while in the Americas[42,56,60,76,97,105,110,127,153] the incidence varies between 11 and 50 percent. Earlier studies with electron microscopy generally found a lower incidence of rotavirus than later results obtained with ELISA[97,105,153]. CFT (Complement fixation)[131], RIA (Radioimmunoassay)[58,152] or I.E.O.P.[146,149] (immunoelectro-osmophoresis) techniques. Although more sensitive, ELISA[165] is regarded as a reliable diagnostic tool especially useful in developing countries[26,66]. It is evident from these figures that rotavirus is an important enteropathogen worldwide which in some areas accounts for more than 50 percent of infantile diarrhoea. The presence of rotavirus in the stool is significant in most instances as it is an unusual finding in controls when these have been studied.

Campylobacter fetus ss jejuni

At the Children's Hospital, Campylobacter fetus ss jejuni emerges as a significant enteropathogen in infants admitted to the rehydration ward. The overall incidence was 18 percent (6,4 percent in controls) with the highest incidence in June of 28,6 percent. There are no previous reports of overall incidence at the Children's Hospital. Due to the fact that the importance of Campylobacter as a cause of childhood diarrhoea has only recently been recognized, there is a relative lack of published data on it's incidence worldwide. In a study of summer diarrhoea in Johannesburg, 15 percent of black children under 2 years

were found to have the organism in their stools[116]. Another study by Bokkenheuser et al[16], also in Johannesburg, reports a 35 percent incidence in similar children. In Bokkenheuser's study a breakdown of the results according to age, reveals that while the incidence in infants up to 8 months of age (31 percent) and those from 9 to 24 months (38 percent) was similar, the incidence in the control groups was different. Campylobacter occurred in only 5 percent of the younger control infants, but in 40 percent of the older group. This suggests that Campylobacter is a more important cause of diarrhoea in the young infant. The results of the present study correspond with those from the infants under 8 months of age in the study just mentioned. Thoren et al[149] in a study from Ethiopia report a 13 percent incidence (3 percent in controls) in children under 2 years with summer diarrhoea. Campylobacter is less common in Britain and Europe, Butzler[25] reports a 5,1 percent incidence in children with diarrhoea (1,3 percent in controls). Relatively few reports from the Americas mention Campylobacter and it does not appear as a significant pathogen in any of the published surveys to date. From the Far East a 4 percent incidence in children under 6 years of age with acute diarrhoea is reported in Thailand[85]. The present study emphasises the apparent significance of Campylobacter as a cause of infantile diarrhoea in the developing world.

Shigella

Shigella occurred in 5,7 percent of the infants with diarrhoea and in only one control (0,3 percent). This is less than the 12,9 percent found by Wittmann and Hansen[159] in a study of similar infants at the Children's Hospital (none isolated in the controls). Other reports from Cape Town reveal a somewhat lower incidence of 2,4 to 5 percent[29,155],

but these are not strictly comparable. In a survey of summer diarrhoea Robins-Browne et al[116] report a 9 percent incidence of Shigella while Koornhof et al[82] in an earlier study from Johannesburg found a 19 percent incidence. In some areas, Shigella is a major cause of diarrhoea. In Egypt, Abraham et al[1] found Shigella in 30 percent of children under 2 years with diarrhoea compared with a 4 percent incidence in the control group. Workers from Pakistan and Bangladesh[9,68] report a 12 to 15 percent incidence of Shigella and in these studies it was the major identifiable enteropathogen. In India[88,128,144] the figures are lower with the incidence varying from 1,8 to 7,4 percent in studies of children mostly under 3 years of age. Shigella is characterised by its extreme infectivity with as few as 10 to 100 organisms capable of producing disease. As a result epidemics due to Shigella are common and this accounts to some extent for the widely fluctuating incidence. Reports from the Americas show a significant incidence of Shigella. Regional epidemics of shiga dysentery have occured in the Latin-American countries such as Guatemala with a high rate of infection and high mortality[97]. Shigella is in contrast an uncommon enteropathogen in Britain and Europe [23,87,121,152,157].

Salmonella

Salmonella is not uncommon in the stools of children with diarrhoeal disease but in the developing countries it is often present with equal frequency in the stools of asymptomatic children. In this study, 10.8 percent of patients and 7,1 percent of controls had a Salmonella in the stool which is not a significant difference. If Salmonella group B is analysed separately there is a statistically significant association

with diarrhoeal disease ($p < 0,01$). Thus certain Salmonella types may be enteropathogens while others are not. Bokkenheuser et al[16] found Salmonella present in 22 percent of controls aged 9 to 24 months but in only 16 percent of similarly aged infants with diarrhoea. Wittmann and Hansen[159] in a study at the Children's Hospital in 1962 found Salmonella in 6,9 percent of patients compared with 5 percent in the controls. Other studies from Cape Town[29,155] without controls report a 3 to 4,5 percent incidence of Salmonella. In their study of summer diarrhoea Robins-Browne et al[116] found Salmonella in 17 percent of black infants but only in 3 percent of the controls showing it to be a significant enteropathogen in this particular survey. Worldwide Salmonella is more common in the developing areas with exceptions being Ethiopia[146,149], where an extensive study failed to isolate any Salmonella, and the Indian subcontinent[9,68,128,144] (Bangladesh, Pakistan and to a lesser extent India) where it is an uncommon enteropathogen. In developed countries[23,87,110,121,127,152,157], Salmonella occurs in small but significant numbers and is often second to rotavirus as an identifiable cause of infantile diarrhoea.

Enteropathogenic E.Coli

Enteropathogenic E.coli was the most frequently isolated bacteria in this study but in many infants their presence appeared to have no correlation with the occurrence of diarrhoea. Of the fifteen serotypes, three: 0126:K71(B16); 0119:K69(B14) and 0127:K63(B8) seem to be enteropathogens when their incidence is compared with that of the control group. EPEC are frequently isolated in children with diarrhoea more especially in developing countries[60,82,105,109]. As with Salmonella they are often present in the stools of children without

diarrhoea. In some South African studies[16,29,48,116], mostly of summer diarrhoea they appear to be a significant cause. In a study from Java[136] there was no difference in incidence between patients and controls, but in others from India[88,128,144] EPEC appeared to be a cause of diarrhoeal disease. It seems that a specific EPEC type may differ in pathogenicity in different areas. Similarly a serotype may vary in significance at different times of the year. In this study EPEC 0126:K71(B16) was a significant enteropathogen overall but during May, June and July there was no statistically significant association with the presence of diarrhoea. This finding may explain why EPEC are found to be significant causes of diarrhoea in some studies and not in others.

Pathogenicity

The variability of the degree of pathogenicity of a particular micro organism is an important concept. As noted above this was found in the case of EPEC 0126:K71. Similar findings were demonstrated for Campylobacter which taken overall was a significant enteropathogen in the present study. During February the pathogenicity of Campylobacter appeared reduced as it was present in 23,8 percent of controls compared with 15,7 percent of patients. Overall Salmonella groups excluding group B were not significantly associated with the presence of diarrhoea. During April, August and February non-group B Salmonellae were isolated more frequently than group B Salmonellae. During this period no Salmonellae were isolated amongst the controls. Although this failed to achieve statistical significance it was suggestive of the non-group B Salmonellae being pathogenic at these times. It is possible that the pathogenicity of many microorganisms in the gut microflora may vary. The pathogenicity may depend on environmental, microbiological

and host factors being favourable. These findings emphasize the absolute necessity of adequate control groups when studying the aetiology of diarrhoeal disease. Without this the interpretation of results may well be impossible, or at least suspect.

It is only possible to speculate as to the reasons for the variability of pathogenicity demonstrated. Two possible mechanisms are evident from a review of the literature. The use of antimicrobial agents may play a role. It has been shown that antimicrobial therapy bears a relationship to subsequent infection with organisms such as Salmonella. Shigella and Vibrio cholerae. Mice were rendered more susceptible to Salmonella infection after oral treatment with streptomycin[173] while in humans Salmonella infection may be exacerbated or activated by antimicrobial agents such as penicillin, ampicillin or tetracyclines[181]. It is unlikely that antibiotic usage would fluctuate in the community to the extent that it could explain the variation demonstrated. A recent report[192] that subtherapeutic dosages of antibiotics used for growth promotion in animal husbandry was responsible for a multi resistant Salmonella gastroenteritis outbreak may suggest a role for antimicrobial agents in the seasonal variation of pathogenicity.

It seems more likely that variation of the organism itself may be a factor. Classic enteropathogenic E.coli serotypes frequently associated with diarrhoea have been shown to adhere to HE_p-2 (human epithelial) cells in tissue culture[178]. The genes coding for HE_p-2 adhesiveness and the ability to adhere to intestinal mucosa are plasmid mediated[169]. This adhesiveness together with the effects of a local cytotoxin are thought to be essential for pathogenicity[225]. Multiple genes encoding for the properties of Shigellae have been shown to be

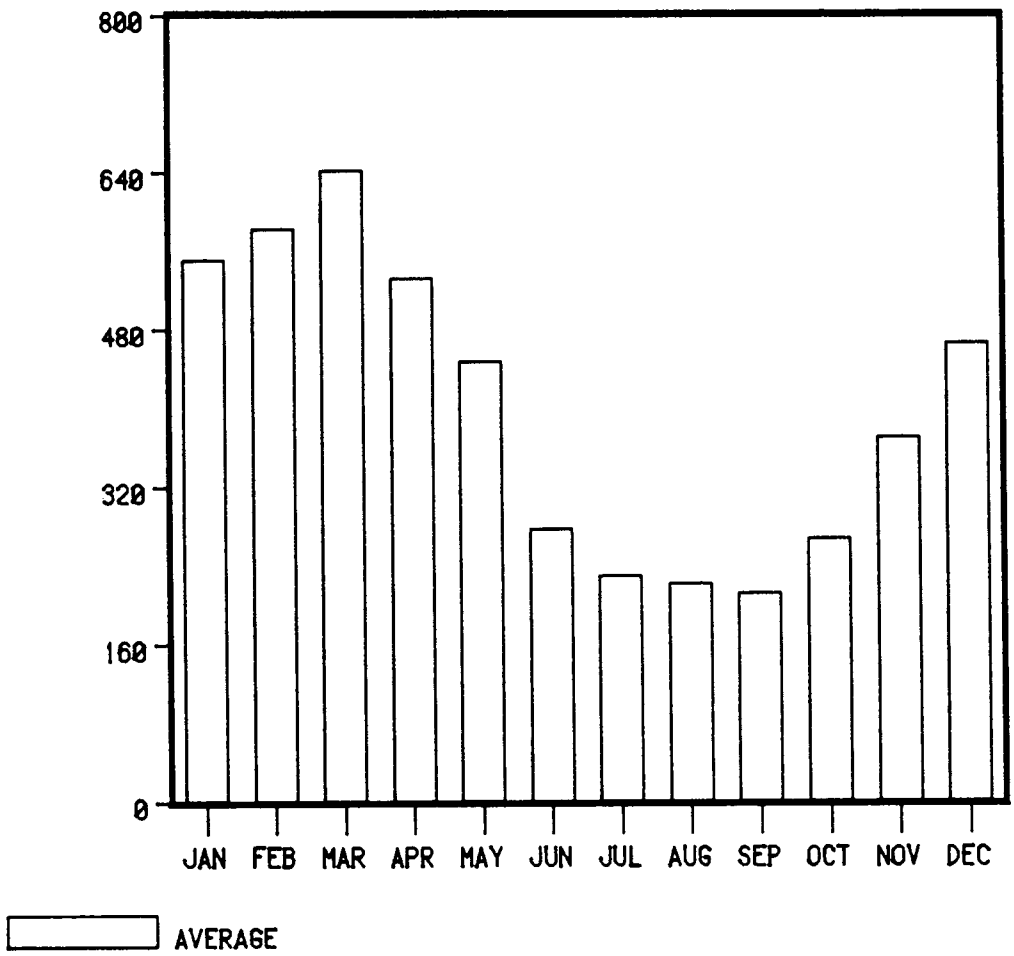
located on very large plasmids[227]. Plasmid mediated pathogenicity may thus account for variations in pathogenicity with time.

Further studies are needed to characterise organisms showing variable pathogenicity. Once again the role of control patients is highlighted as the above and other factors could be compared between the patient and control groups.

Seasonal Variation

The monthly rate of admissions to the rehydration ward of the Children's Hospital has an almost constant seasonal variation (Figure 6.14). Diarrhoeal disease in Cape Town in the Coloured and Black population groups is characterised by a marked summer peak in incidence with a definite winter trough. The climate of the Cape Peninsula where the hospital is situated and the area from which the majority of the hospital's patients orginate is Mediterranean in character. The summers are warm and relatively dry while the winters are cool and wet. Most diarrhoeal disease in the developing world occurs in the warm summer months[1,97,144], while in the developed countries diarrhoea in children occurs more frequently in winter[108]. The results of this study reflect that of a developing area. Most Southern African studies[116,117], reporting experience amongst black children in Johannesburg, show this high summer incidence. It seems that in tropical and sub-tropical climates the seasonal variation is less marked[104,110]. Reports from India and elsewhere in the Far East[9,40,85,88,128,144] indicate that the months before the monsoons are associated with a higher incidence of diarrhoeal disease, while in Ethiopia[146,149] most cases occur at the beginning of the rainy season. (Spring to Summer).

Figure 6.14 AVERAGE ADMISSIONS 1976-1981.



A single study from Rhodesia[32] shows a significant winter peak with many cases due to rotavirus. Another anomaly of that report was the overall low incidence of diarrhoeal disease (around 200 admissions per year) corresponding to that of a more developed area. Indeed significant numbers of the infants in the study were white. In a study from Houston and Mexico City, Pickering et al[110] found no variation in either the number of cases or the incidence of rotavirus throughout one year. Surveys from England[70,87] and America[56,60,76] confirm the winter peaks in diarrhoeal disease of developed countries.

In this survey rotavirus occurred mostly from late summer to winter with a low incidence in spring and mid-summer. Rotavirus was nevertheless present throughout the year. It is difficult to explain why rotavirus occurred more frequently in the control group during October and December, when it was uncommon in the patients.

Campylobacter did not show as marked a seasonal variation as rotavirus but was also more frequent in the cooler wet months from May to August. There is no published data relating to the seasonal or climatic variation in the incidence of Campylobacter. Salmonella and Shigella were present throughout the year but lacked a significant seasonal trend. Significant EPEC occurred constantly throughout the year with a slight increase in December and January (mid-summer) (Figure 6.11B). A direct comparison of these results with published data is not possible as these studies have mostly been limited to periods of high incidence.

Monthly analysis of those patients with significant positive stool isolates (Figures 6.11B and 6.12) indicate a high detection rate in the winter months (June 59,5 percent and July 69,2 percent). This is a

period when admissions to the rehydration ward are lowest. During the summer months November to March when diarrhoeal disease is most common in Cape Town the detection rate of significant isolates is lowest (less than 50 percent). This seasonal variation is less obvious if all the potential enteropathogens isolated are included (Figure 6.11A). In this case the detection rate in the winter months remains high (July 77 percent and August 80 percent) but the number of positive isolates in the summer months January to March rises considerably (over 70 percent now positive).

An important fact emerges from a comparison of the detection rate of patients with positive isolates of potential enteropathogens with that of those positive for significant enteropathogens. For the months January, February and March a period of high incidence of diarrhoeal disease 20 to 30 percent of patients have potential enteropathogens in their stools which appear of no significance (Figure 6.13A). In contrast during the winter months (June and July) when diarrhoea is least common only 7 percent of potential enteropathogens in the stools are not significant. The detection rate of enteropathogens in the controls parallels these findings with most in the summer months and least in the mid-winter months of June and July (Figure 6.13B). The findings described above may be interpretted as indicating a degree of environmental contamination in the warm summer months. This bacterial contamination may itself cause the diarrhoea or alternatively predispose to the action of other factors causing the diarrhoea. Further work is needed to substantiate this hypothesis. From the findings of this study no definite cause was found for the characteristic summer peak in the incidence of infantile infectious diarrhoea in Cape Town.

Multiple Enteropathogens

Multiple enteropathogens are more common in developing areas[85,116,146,149], and are reported in 10 to 30 percent of patients with acute diarrhoea. In contrast surveys from Britain and America show multiple pathogens in less than 5 percent [87,110,157]. While the majority of patients had single isolates from the stool, multiple isolates occurred relatively frequently. Single isolates of significant organisms occurred in 39,3 percent of patients while two or more were isolated in 10,1 percent. An identifiable significant enteropathogen was present in 49,4 percent of patients with diarrhoea leaving the balance of 50,6 percent in whom no significant enteropathogen was identified in the stool. If all the organisms or potential enteropathogens isolated in this study are included, 43 percent of patients had one organism and 23 percent had two or more organisms present in the stool. Robins-Brown et al[116] in their study identified potential pathogens in 69 percent of patients with summer diarrhoea. Many studies which include rotavirus now identify pathogens in the stools of over 50 percent of cases[23,42,60,87,116,149,152].

CONCLUSIONS

In conclusion a study of the enteropathogens identified by this survey of infants aged 6 weeks to one year admitted to the Children's Hospital over one year shows the following:

1. Campylobacter fetus ss jejuni and rotavirus were the single most important enteropathogens. Shigella, Salmonella group B, Yersinia entercolitica, EPEC types 0126:K71(B16), 0119:K69(B14)

and 0127:K68(B8) were identified as significant but less important enteropathogens.

2. Variability of the degree of pathogenicity with time was demonstrated for EPEC 0126:K71, Campylobacter and the non group B Salmonellae

3. Rotavirus and Campylobacter were more common in the cooler wet months. None of the other enteropathogens had a significant seasonal variation.

4. An identifiable cause for the diarrhoea was found in 49,4 percent of patients if only significant enteropathogens were included. A potential enteropathogen was present in the stools of 66 percent of the infants studied.

5. The highest percentage of patients with positive stool isolates was found in the winter months corresponding to the period of lowest incidence of diarrhoeal disease. The opposite was found in summer when the incidence of diarrhoeal disease was at its peak.

6. No cause was found for the marked summer peak in the incidence of diarrhoeal disease in Cape Town. It is suggested that in summer a high degree of environmental contamination exists in the community from which these infants originate. This is supported by the high incidence of carriers of potential enteropathogens in both patients and controls during this period. An hypothesis is put forward that this environmental

contamination predisposes to or is associated with factors (possibly viral in nature) that act to produce the characteristic summer peak.

7. Multiple enteropathogens occurred relatively frequently (23 percent) which is characteristic of a developing community.

CHAPTER 7

CLINICAL FEATURES ASSOCIATED WITH THE PRESENCE OF SIGNIFICANT ENTEROPATHOGENS AND FACTORS ASSOCIATED WITH PERSISTENCE OF ACUTE DIARRHOEA

To determine if infection with specific enteropathogens could be identified on clinical grounds the relationships between clinical data reported in Chapter 5 and enteropathogens identified as significant in Chapter 6 were analysed. Factors predisposing to persistent or more chronic diarrhoea after the initial acute attack were also noted.

RESULTS

7.1. CLINICAL FEATURES RELATED TO THE ISOLATION OF SIGNIFICANT ENTEROPATHOGENS

7.1.1. Race, Age and Duration of Diarrhoea:

These results are shown in Table 7.1. There was no statistically significant difference in the incidence of enteropathogens isolated from Coloured and Black children. Age influenced the incidence of Campylobacter, Salmonella group B (hereafter referred to as Salmonella) and Shigella.

Campylobacter and Shigella were more common in those older than six months but only in the case of Campylobacter did this achieve statistical significance (X^2 3,9 $p < 0,05$). Salmonella was more common in infants under six months (X^2 4,34

TABLE 7.1

SIGNIFICANT ENTEROPATHOGENS[1] VERSUS RACE, AGE AND DURATION OF DIARRHOEA BEFORE ADMISSION

All patients	229	316	302	243	23%	49%	28%
Organism	Race		Age		History of Diarrhoea		
	Coloured % Incidence	Black % Incidence	< 6 mths % Incidence	> 6 mths % Incidence	< 2 days %	2-4 days %	> 4 days %
Campylobacter n = 98	15%	++20%	15%	*22%	21%	51%	28%
Rotavirus n = 89	17%	16%	15%	18%	26%	53%	21%
Salmonella group B n = 29	6%	5%	**7%	3%	38%	38%	22%
Shigella Significant types n = 28	6%	5%	4%	+7%	23%	42%	35%

1 Significant enteropathogens as defined in Chapter 6

* More infants with Campylobacter > 6 months X^2 3,9 $p < 0,05$

** More infants with Salmonella group B < 6 months X^2 4,34 $p < 0,05$

\+ More infants with Shigella 6 months but not statistically significant X^2 1,38 $p = 0,24$

++ Difference not statistically significant X^2 1,64 $p = 0,02$

$p < 0,05$). There was no significant difference in the duration of diarrhoea before admission to the rehydration ward in patients from whom different enteropathogens were isolated in the stool.

7.1.2. Percentage of Expected Weight, Upper Respiratory Tract Symptoms, Axillary Temperature and Clinical Degree of Dehydration

Rotavirus occurred more frequently in well nourished infants (X^2 3,9 $p < 0,05$). There was no significant difference in the incidence of other enteropathogens (Table 7.2) between infants with a bodyweight less than 80 percent of expected and those with a weight greater than 80 percent of expected bodyweight. There was no significant association between upper respiratory tract symptoms, axillary temperature $> 37,5°C$, clinical degree of dehydration and any of the enteropathogens listed in Table 7.2. Rotavirus was associated with significantly less upper respiratory tract symptoms than the group as a whole (X^2 8,65 $p < 0,005$).

7.1.3. Convulsions

Convulsions were common (8). Rotavirus, Campylobacter and an EPEC respectively were isolated from the stools of three of the patients who had a convulsion. None had a Shigella isolated from the stools.

TABLE 7.2

SIGNIFICANT ENTEROPATHOGENS[1] AND CLINICAL FEATURES

All patients n = 545	173	357 n = 530	25%	22%	29%	67%	4%
Organism	% expected wt < 80%	% expected wt >80%	Upper Resp Tract Symptoms	Axillary Temp n = 520	Clinical degree of dehydration		
	% incidence			> 37,5°C	0- <5%	5-10%	>10%
Campylobacter n = 98	18%	18%	17%	15%	32%	65%	3%
Rotavirus n = 89	12%	+19%	*12%	24%	31%	69%	0%
Salmonella Group B n = 29	7%	5%	14%	7%	28%	72%	0%
EPEC Significant Types n = 80	17%	14%	23%	21%	16%	75%	9%
Shigella Significant Types n = 28	5%	6%	36%	16%	29%	71%	0%

1 Significant enteropathogens as defined in Chapter 6

\+ Significantly more infants > 80% Expected wt X^2 3,9 $p < 0,05$

* Rotavirus significantly less URTI symptoms X^2 8,65 $p < 0,05$

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7.1.4. Faecal Leucocytes

Faecal leucocytes were an unusual finding (4 percent). Ten of the 22 patients (45,5 percent) with pus cells on stool microscopy had a Campylobacter present in the stool. This association was statistically significant (X^2 9,87 $p < 0,002$). No patient in whom rotavirus was isolated had leucocytes in the stools.

7.1.5. Haematological Parameters

A leucocytosis ($>$ 20 000 leucocytes per cubic millimeter) was most frequent in patients from whom Salmonella was isolated. Patients from whom rotavirus was isolated had the lowest incidence of leucocytosis and this was the only statistically significant difference noted (X^2 4,32 $p < 0,05$). Toxic granulations and a left shift were significantly more common when Shigella was isolated (X^2 4,22 $p < 0,05$). Atypical lymphocytes were found in between 12 and 19 percent of patients from whom different enteropathogens were isolated. No significant difference was noted for the various enteropathogens. These results are shown in Table 7.3.

7.2. PARENTERAL CAUSES OF DIARRHOEA

Clinically significant systemic or parenteral disease that could be considered responsible for the acute diarrhoeal illness was found in 124 patients (23 percent). If those patients in whom significant enteropathogens had been isolated from the stools

TABLE 7.3

SIGNIFICANT ENTEROPATHOGENS[1] AND HAEMATOLOGICAL PARAMETERS

ORGANISM	LEUCOCYTE COUNT > 20 000 CELLS PER mm^3	ATYPICAL LYMPHOCYTES PRESENT	LEUCOCYTE TOXIC GRANULATIONS AND LEFT SHIFT
Campylobacter n = 98	16%	12%	42%
Rotavirus n = 89	*8%	11%	**26%
Salmonella Group B n = 29	24%	17%	41%
EPEC significant types n = 80	16%	14%	40%
Shigella significant types n = 28	13%	19%	+64,5%

1 Significant enteropathogens as defined in Chapter 6

* Leucocytosis less common X^2 4,32 $p < 0,05$

** Toxic granulations and left shift less common
X^2 4,22 $p < 0,05$

\+ Toxic granulations and left shift more common
X^2 10,36 $p < 0,002$

TABLE 7.4

POSSIBLE PARENTERAL CAUSES OF ACUTE DIARRHOEA

CAUSE	TOTAL (PATIENTS)	ASSOCIATED WITH SIGNIFICANT ENTEROPATHOGEN[1]	SOLE INDENTIFIABLE CAUSE
Bacteraemia/ Septicaemia	16	13	3
Significant respiratory pathology[2]	47	24	23
Urinary Tract infection[3]	53	33	20
Measles	8	5	3
TOTAL	124	75	49

1. Significant enteropathogen as previously defined
2. Lobar or diffuse bronchopneumonic consolidation and/or marked airtrapping
3. Pure urinary culture and/or $>$ 10 WBC/hpf

are excluded, there remain 49 patients (9 percent) in whom a parenteral factor could have been the cause of the diarrhoeal illness. These results are shown in Table 7.4.

7.3. FACTORS ASSOCIATED WITH CHRONICITY OF DIARRHOEA:

The following criteria were used to determine persistent or more chronic diarrhoea:

i. Patients remaining longer than 4 days in the rehydration ward

The 4 day cut off point was used as at this time a standard management regime utilised at the Children's Hospital for ongoing diarrhoea commences[20] (i.e. a change of feed to a soy-based formula). At seven days protein and fat losses in the stools are already such that maintenance of nutrition necessary for repair of the intestinal mucosal damage is unlikely[94]. The more widely accepted definition of persistent or protracted diarrhoea, that is diarrhoea persisting for 14 days accompanied by a constant or decreasing body mass[233,201] would exclude many infants with significant persistent diarrhoea.

ii. Admission to an inpatient bed elsewhere in the hospital from the rehydration ward as a result of ongoing diarrhoea

The duration of hospital stay as reflected in Table 5.13 was not analysed separately as in many cases factors other than ongoing diarrhoea resulted in additional prolongation of the hospital stay. These factors included inability to

trace the parents, other systemic disease and management of severe protein energy malnutrition.

iii. Previous admission to the rehydration ward for acute dehydrating diarrhoea

This indicated that the patient had had at least two episodes of diarrhoea (in some instances more) and suggested the possibility of more chronic diarrhoea.

iv. Readmission within the 6 month follow-up period to the rehydration ward for acute dehydrating diarrhoea

Only a hospital readmission for diarrhoea was accepted as evidence of a relapse on the diarrhoea. Reports in the hospital files from the various community health sisters regarding a relapse of the diarrhoea were uncorroborated, possibly subjective and available only in the minority of patients. These reports were not used to assess ongoing diarrhoea or a relapse.

7.3.1. Nutritional Status

Patients underweight for age more often required admission to an inpatient ward bed for management of persistent diarrhoea. This was most pronounced in those with a bodyweight less than 60 percent of expected (Table 7.5). These differences were statistically significant (X^2 42,16 $p < 0,0001$). Similarly patients staying longer than 4 days in the rehydration ward were more likely to be underweight for age than those discharged by

TABLE 7.5

NUTRITION VERSUS CHRONICITY OF DIARRHOEA

NUTRITONAL STATUS % EXPECTED WT	PATIENTS REQUIRING INPATIENT WARD ADMISSION n = 90	PATIENTS REQUIRING READMISSION TO THE REHYDRATION WARD n = 83	PATIENTS PREVIOUSLY ADMITTED REHYDRATION WARD n = 74
< 60%	44%[1]	21%[2]	18%[3]
60 - 80%	28%[1]	12%	
80 - 120%	10,3%	17%	12%
> 120%	5,9%	12%	

1. Significantly higher admission rate X^2 42,16 $p < 0,0001$
2. Not statistically significant X^2 0,33 $p = 0,3$
3. Not statistically significant difference X^2 3,01 $p = 0,08$

the fourth day (Table 7.6) (X^2 4,43 $p < 0,05$). There was no association between poor nutritional status and recurrence of diarrhoea as indicated by previous admissions or by subsequent readmissions to the rehydration ward (Table 7.5).

7.3.2. Previous Episodes of Diarrhoea

Patients who had previously been admitted to the rehydration ward more often remained for longer than 4 days in the rehydration ward than those infants never previously admitted (22 percent versus 12 percent). This was a statistically significant difference (X^2 7,13 $p < 0,01$). A history of previous admission to the rehydration ward was associated with a significantly higher incidence of subsequent admission to a hospital ward for management of persistent diarrhoea (X^2 4,73 $p < 0,05$)

7.3.3. Enteropathogens Isolated

Overall patients with significant enteropathogens (Table 7.7) isolated in the stool cultures were more often admitted to a hospital ward (X^2 9,5 $p < 0,002$). In particular those with Salmonella in the stool isolates were more often admitted (X^2 8,95 $p < 0,01$). Patients with rotavirus and Shigella isolated from the stools were admitted less often than patients in whom other significant enteropathogens were isolated (X^2 4 $p < 0,01$). Patients with rotavirus had less frequently been previously admitted to the rehydration ward or subsequently required admission to the rehydartion ward but this difference was not statistically significant.

TABLE 7.6

NUTRITION VERSUS DURATION OF STAY IN REHYDRATION WARD

NUTRITIONAL STATUS % EXPECTED WEIGHT	REHYDRATION WARD < 4 DAYS n = 437		REHYDRATION WARD > 4 days n = 93	
< 60%	5%	)	12%	)
		) 30,5%		) 42%*
60 - 80%	25,5%	)	30%	)
80 - 120%	66%	)	56%	)
		) 69,5%		) 58%
> 120%	3,5%	)	2%	)

* X^2 4,43 $p < 0,05$ significant difference

TABLE 7.7

ENTEROPATHOGENS VERSUS CHRONICITY OF DIARRHOEA

ENTEROPATHOGEN	PATIENTS REQUIRING WARD ADMISSION	PATIENTS REQUIRING READMISSION TO REHYDRATION WARD	PATIENTS PREVIOUSLY ADMITTED TO REHYDRATION WARD
Campylobacter n = 98	25%	18%	15%
Rotavirus n = 89	+13%	*10%	**9%
Salmonella Group B n = 29	++38%	28%	21%
EPEC Significant n = 80	29%	21%	19%
Shigella significant types n = 28	+10%	19%	14%
All significant Enteropathogens n = 269	+++23%	17%	15%
No Significant Enteropathogens n = 276	12%	13%	12%

\+ Admission rates significantly less X^2 4,1 $p < 0,01$

++ Admission rate significantly higher X^2 8,95 $p < 0,01$

+++ Admission rate higher than those without enteropathogens X^2 9,5 $p = 0,002$

* Not significant X^2 2,29 $p < 0,1$

** Not significant X^2 2,18 $p < 0,1$

7.3.4. Number of Organisms Isolated

There was no difference in the frequency of chronicity between those with a single organism isolated in the stool and those from whom multiple enteropathogens were isolated (Table 7.8).

7.3.5. Season

More patients were transferred to an inpatient ward bed for management of persistent diarrhoea during the winter and spring months compared to the summer and autumn (25 percent versus 14 percent). These results are shown in Table 7.9 and demonstrate a statistically significant difference (X^2 13,9 $p < 0,001$).

TABLE 7.8

CHRONICITY VERSUS NUMBER OF ORGANISMS ISOLATED

ORGANISMS CULTURED	STAY IN REHYDRATION WARD > 4 DAYS	WARD ADMISSION
None	17%	12%
One	18%	23%
More than one	16%	20%

TABLE 7.9

WARD ADMISSION VERSUS SEASON[1]

PATIENTS n = 545	WINTER/SPRING	SUMMER/AUTUMN
Admitted to ward from rehydration ward	58 (24,6%)*	37 (12%)
Discharged home from rehydration ward	178	272

1 Winter/Spring: May - October
Summer/Autumn: November - April

* Significant difference in admission rate
X^2 13,9 $p < 0,0005$

DISCUSSION

It is generally accepted that the clinical features of acute infectious infantile diarrhoea differ little despite a variety of aetiological factors. In the present study the clinical features were indistinguishable for the group as a whole (Chapter 5). Further analysis of the clinical data presented in this chapter confirmed that the clinical picture is remarkably similar despite the isolation of different enteropathogens.

Despite differing environmental backgrounds there was no significant difference in Coloured and Black infants as regards the incidence of the various enteropathogens (Table 7.1). There was a higher frequency of isolation of Campylobacter in the Black infants but this did not achieve statistical significance (X^2 1,64 p = 0,2).

Age influenced the incidence of Campylobacter and Salmonella group B. Campylobacter was more common in infants older than 6 months while Salmonella was more frequent under 6 months of age. Bokkenheuser et al[16] identified Campylobacter as a significant cause of acute diarrhoea under 9 months of age in South African Blacks. Beyond this age the micro organism was equally common in patients and controls. Similar findings were reported by Richardson et al[115] in a study from the same hospital in Soweto South Africa. In contrast Campylobacter remained a significant enteropathogen during the whole of the first year of life the present study. No explanation of this difference is apparent but Campylobacter is identified in all studies as an important cause of acute infectious diarrhoea in the young infant.

Rotavirus was more frequently isolated in well nourished infants and associated upper respiratory symptoms were infrequent amongst these patients (Table 7.2). Respiratory tract symptoms have previously been reported in association with rotavirus infection[87,147] although the virus has not been isolated from the respiratory tract. Another study[34] found no characteristic clinical features associated with rotavirus diarrhoea. In the present study rotavirus had the lowest frequency of associated respiratory symptoms when compared with other enteropathogens. Clinial identification of rotavirus infection on these grounds was not possible as claimed by Lewis et al[87].

Shigella, which is described as having an increased incidence of associated fever and convulsions[4,77] due to a heat labile toxin, was not associated with convulsions and fever was infrequent. Most children with convulsions due to shigellosis reported by Ashkenazi et al[4] were aged between 1 and 4 years. This is also the age distribution characteristic of febrile convulsions which are uncommon during the first year of life[46]. Presuming that fever is an important precipitating factor it is not unexpected that convulsions are infrequent with shigellosis under a year of age.

Stool microscopy is regarded as important by some workers in the diagnostic work-up of acute diarrhoea[59]. Bacteria known to penetrate the mucosa such as Campylobacter, Salmonella, Shigella and invasive E.coli are potential causes of faecal leucocytes. It is suggested that an absence of faecal leucocytes may enable rapid identification of viral or non-specific diarrhoea[59]. Specific stains (methylene blue) for faecal leucocytes were not used in the present study and the actual incidence may have been higher than the 4 percent recorded.

Campylobacter had a statistically significant association with the presence of faecal leucocytes (X^2 9,87 $p < 0,002$) while this was not demonstrated for Salmonella or Shigella. From this and the results reported by Abraham et al[1] faecal leucocytes cannot be recommended for the identification of viral and non-specific diarrhoea. The presence of faecal leucocytes may be suggestive of a Campylobacter infection.

Haematological parameters (leucocytosis, toxic granulations and a left shift of polymorphonuclear leucocytes) which indicate a bacterial infection were common in patients with bacterial enteropathogens particularly Shigella. They were less frequent when rotavirus was isolated. These parameters are non-specific indicators of stress such as infection, metabolic upset or shock and do not enable clinical differentitation of the respective bacterial causes of acute diarrhoea. Their absence suggests a viral aetiology but is not of sufficient specificity to allow a confident differentiation of bacterial and viral aetiologies. Atypical lymphocytes despite their recognized association with viral infections were of no predictive value. The findings suggest that these haematological parameters have little value in differentiating between the various causes of acute infectious infantile diarrhoea.

The aim of reviewing the clinical data in relation to the enteropathogens isolated was to determine if there were features distinguishing between patients with different enteropathogens. Candy[26] has suggested that common agents causing diarrhoea can be identified on clinical grounds alone (Table 1.3, Chapter 1). Other studies from Ethiopia and India have been unable to separate aetiological agents on clinical grounds[88,149]. In the present study

some clinical differences were demonstrated between certain enteropathogens but these were not striking enough to be clincally useful. While it is tempting to offer the doctor without adequate laboratory facilities a means of suspecting the probable aetiological agent, this would appear to be unreliable for the young infant.

The role of parenteral disease in acute infantile diarrhoea is controversial but most feel that it indeed plays a role[26,138]. In the present study only 9 percent of patients had parenteral disease as the sole identifiable possible cause of the acute diarrhoeal episode. A definite causal relationship to the diarrhoea cannot be assumed as there may have been an unidentified enteral factor. It would appear that parenteral factors are relatively unimportant in the causation of acute infantile diarrhoea.

A major source of morbidity and mortality in patients with acute infectious infantile diarrhoea is persistence of the diarrhoea. Acute and particularly recurrent or chronic diarrhoea have been shown to be initiating factors in the development of protein energy malnutrition[3,30,122]. Malnutrition itself may be a determining factor in diarrhoeal disease. This was highlighted by Wittman and Hansen[159] who found that diarrhoeal disease has a tendency to become chronic in malnourished children from poor socio-economic environments. Black et al[10] found that thin children (i.e. low weight for length) under 24 months of age had a longer duration of diarrhoea than better nourished children. In his study children of differing nutritional states had similar incidences of diarrhoea. James[71] reported from Costa Rica that in children 1 to 36 months of age the number of attacks was the same for both malnourished and normal weight children. Beyond this age

malnourished children had double the rate of diarrhoeal episodes of normally nourished children. In contrast to Black et al's[15] findings there was no increase in the duration of diarrhoea in the malnourished group under one year of age. Over one year of age both Black et al and James found the attacks significantly prolonged in malnourished children. In the present study children who were underweight for age more often developed persistent, more chronic diarrhoea. This is similar to the findings of Wittmann and Hansen but contrary to those of James. It is in agreement with the report of Black et al as regards duration of diarrhoea but differs in that recurrence was more frequent in the present study in the underweight group. Underweight for age is confirmed as a factor promoting chronicity of diarrhoea.

The presence of significant enteropathogens was in general associated with a higher incidence of hospital inpatient ward admission (X^2 9,5 $p<$ 0,005) when compared to those infants from whom no micro-organisms were isolated in the stools. Maiya et al[88] found both Salmonella and Shigella to be associated with more protracted diarrhoea but not in those where EPEC types were isolated. Significantly more persistent diarrhoea occurred with Salmonella in the present study but the opposite occurred when Shigella was isolated. Norrie[109] states that the spectrum of Campylobacter enteritis is wide varying from asymptomatic carriage to severe systemic illness but that in most the disease is moderate resolving within a week. In the present study 25 percent of patients with Campylobacter developed more chronic diarrhoea requiring transfer to an inpatient bed.

Rotavirus and Shigella were associated with a significantly lesser incidence of chronic or persistent diarrhoea. Rotavirus was confirmed

as a cause of acute self-limiting diarrhoea as reported previously [87,96,147]. It was associated with the lowest incidence of previous admission (9%) as well as subsequent admission (10%) to the rehydration ward.

Multiple micro-organisms isolated from the stools were also considered as a possible factor producing chronicity. The present study demonstrated that although common they were not associated with persistent or chronic diarrhoea. Multiple enteropathogens are frequently reported from developing areas [1,116] but no comment is made regarding their relationship to persistence of diarrhoea in these studies.

Admissions to the rehydration ward follow the characteristic summer peak of acute infectious diarrhoea in Cape Town. Transfers from the rehydration ward to an inpatient bed for management of more chronic diarrhoea demonstrated an inverse relationship to the admissions to the rehydration ward. More infants were transferred in winter and spring (May to October) when rehydration ward admissions were lowest. This statistically significant difference (X^2 13,4 $p < 0,001$) could be explained by a greater availability of inpatient beds allowing more of the survey patients to be tranferred. If this were the case one would expect a larger number remaining in the rehydration ward for prolonged periods in summer. It is of interest that the stay of patients in the rehydration ward did not differ significantly during the two periods. During winter and spring 38% were discharged after 2 days and 44% after 4 days while during summer and autum percentages were 34% and 48% respectively. During winter and spring the highest incidence of positive stool isolates of the significant micro-organisms occurred

(Figure 6.11B, Chapter 6). As discussed above these patients were more frequently admitted and it is possible that this was the major contributory factor to the higher frequency of ward admissions during this period. This somewhat unexpected finding has been noted in previously published surveys.

CONCLUSIONS

1. The clinical features of acute infectious infantile diarrhoea in the patients studied were non-specific. There was no typical clinical presentation associated with any of the enteropathogens found to be significant in this study. It is concluded that the clinical picture is of little practical value in the differentiation of possible aetiological agents.

2. Certain associations or lack thereof were noted:

   a. Campylobacter was isolated more frequently from infants over 6 months of age. It was isolated from 45 percent of patients with pus cells on stool microscopy but these constituted only 10 percent of the patients from whom the organism was isolated.

   b. Rotavirus was more frequently isolated in well nourished infants but was not associated with respiratory tract symptoms. Rotavirus was least often associated with haematological indicators of infection such as a leucocytosis, toxic granulations and left shift of the polymorphonuclear leucocytes.

c. Salmonella group B was more often isolated from infants under 6 months of age.

d. Shigella was frequently associated with toxic granulations and a left shift of the polymorphonuclear leucocytes. No association between Shigella and convulsions or fever was demonstrated.

3. Several factors predisposed to more chronic diarrhoea:

a. Malnutrition was confirmed as a factor leading to chronicity of diarrhoea.

b. Previous episodes of diarrhoeal disease requiring admission to the rehydration ward likewise increased the chance of more chronic diarrhoea.

c. Campylobacter, Salmonella group B, and the significant EPEC types were more often associated with chronic diarrhoea. In contrast rotavirus and Shigella infections were acute self-limiting diarrhoea in the majority of cases.

d. A seasonal variation in the frequency of transfers to an inpatient ward bed was noted. The higher frequency of transfers in winter and spring during periods of low diarrhoeal incidence was not satisfactorily explained.

CHAPTER 8

FINAL CONCLUSIONS

A primary aim of this study was to characterise those infants admitted to the Children's Hospital with acute dehydrating diarrhoea. They were relatively well grown and nourished and in most (75 percent) this was the initial diarrhoeal episode. Clinical features of acute infectious infantile diarrhoea in the infants studied were similar regardless of aetiology. Most had an acute history of diarrhoea and vomiting. Over 70 percent were more than 5 percent dehydrated. The clinical assessment of both dehydration and metabolic acidosis was often unreliable. Fever (29 percent) and involvement of the respiratory tract (30 percent) were common. Serum electrolytes and acid base status were frequently abnormal and metabolic acidosis, hyponatraemia and hypokalaemia were the most common disturbances. The high incidence of hypoalbuminaemia found in these children suggests that the acute diarrhoeal episode was a significant nutritional insult.

Bacterial invasion was uncommon with blood cultures positive in only 5 percent. In most infants the disease was an acute, self-limiting and rarely fatal condition. In some (16 percent) the diarrhoea persisted while in others (15 percent) a recurrence of diarrhoea necessitated readmission to hospital. The need for preventitive measures and prompt appropriate therapy of acute diarrhoea in young children is emphasized by these findings. Their importance in the prevention of protein energy malnutrition is also stressed. Inadequacies in the management of these children prior to hospitalisation were highlighted. Early effective oral rehydration both at home and in primary care facilities is recommended.

The second aim was to define the type of communities from which the patients originated. Most infants were born in a hospital or clinic. Amongst the Coloured infants a higher incidence of low birthweight infants (25 percent) was identified. This predisposed to their being underweight at a later stage. Both groups were economically disadvantaged with most incomes below the Household Subsistence Level. Housing was often inadequate and overcrowded.

Differencs between the two racial groups were demonstrated. Coloured parents were younger, less often married, somewhat better educated and had smaller families. The incidence of breast feeding was extremely low amongst Coloured mothers. Black parents were older, more often married and had larger families. The incidence of breastfeeding was low but higher than in the Coloured group. Black families in particular came from a squalid inadequate environment and had more sibling deaths many as a result of diarrhoeal disease. The Coloured communities were more permanent whilst Blacks originated from a largely migrant population.

From these findings it is concluded that the problems facing the two racial groups are different and therefore the type of intervention must of necessity be different. Amongst the Black group who originated from a localised area a home based oral rehydration therapy program is likely to be highly cost effective. This may be less so amongst the Coloured group who were more dispersed. For the Coloured group identification of families at risk, promotion of breastfeeding and general health education were identified as a priority. Improvement of the general socio-economic and environmental conditions of the Black group is necessary to reduce the incidence of acute diarrhoea amongst Black infants.

Thirdly, this study was undertaken to determine the identifiable causes of acute dehydrating diarrhoea in young children admitted to the rehydration ward. Parenteral disease which potentially could result in acute diarrhoea was identified in 23 percent but was probably only relevant in 9 percent. Enteral factors were identified in 66 percent but regarded as significant in 49 percent. Potential enteral pathogens were identified in 66 percent but regarded as significant in 49 percent. Campylobacter fetus ss jejuni and rotavirus were the most important enteropathogens isolated. Together with Shigella, Salmonella group B, EPEC types 0126:K71(B16), 0119:K69(B14) and 0127:K68(B8) and Yersinia entercolitica, these micro-organisms were found to have a statistically significant association with acute diarrhoea when compared with control infants. Multiple enteropathogens were cultured from stools relatively frequently (23 percent) which is characteristic of a developing community.

Campylobacter and rotavirus were isolated in 31 percent of patients with acute diarrhoea. Other significant enteropathogens mentioned above together contributed a further 18 percent of which the enteropathogenic E.coli were the largest subgroup. Parenteral factors constituted 9 percent of the identifiable factors leaving 42 percent in whom no cause for the diarrhoeal illness was found.

Variability of pathogenicity of certain micro-organisms was clearly demonstrated. Campylobacter a significant enteropathogen during most of the study was no longer statistically associated with diarrhoea for short periods when the incidence of this micro-organism was higher in the controls. The converse was true for EPEC 0126:K1 and non group B Salmonella which overall were not significantly associated with acute

diarrhoea but for limited periods assumed this relationship. This emphasizes the need for controls in all similar studies of diarrhoeal aetiology.

The fourth aim was to determine the seasonal pattern and clinical picture associated with each of the respective causes. The incidence of acute infectious infantile diarrhoea has a marked seasonal variation in the Children's Hospital. Peak incidence is during the hot dry summer and the lowest incidence during the cold wet winter. Rotavirus and Campylobacter were more common in the cooler wet months. None of the other enteropathogens had a significant seasonal variation.

The highest percentage of patients with positive isolates was found in the winter months. The opposite occurred during summer when the incidence of diarrhoeal disease was highest and the summer peak seen in Cape Town remains unexplained. A high incidence of patients with non-significant micro-organisms occurred during this period. An hypothesis is advanced that this is the result of environmental contamination and that this contamination may in turn be associated with additional factors that act to produce the characteristic summer peak of diarrhoeal disease.

No typical clinical presentation was associated with any of the enteropathogens found to be significant in this study. It is concluded that the clinical features are of little practical value in the differentiation of a possible aetiological agent. The reported association of rotavirus with respiratory tract symptoms was not confirmed. Likewise the association between Shigella and convulsions was not found. The age of the patients studied (less than one year) may be partly responsible for these differences.

Finally the relative importance of the various aetiological and associated factors with respect to mortality and morbidity was to be determined. Mortality was extremely low with an overall rate of 1,5 percent. It was thus not productive to consider factors associated with mortality. Morbidity was determined by consideration of the length of stay in the rehydration ward, transfer out of the rehydration ward to an inpatient hospital bed for longer term management of persisting diarrhoea or readmission to the rehydration ward with a further episode of diarrhoea. Factors found to have a statistically significant association with continuing diarrhoea and morbidity were bodyweight (underweight for age), previous episodes of diarrhoea, significant enteropathogens (Campylobacter, Salmonella group B and significant EPEC) and the time of year. Rotavirus and Shigella infections most often resulted in an acute self-limiting diarrhoea.

From the conclusions outlined above it is clear that the aims of this study were met. The results obtained provide information not previously available about a disease that occurs frequently in the Cape Town area. This study was limited to infants under one year of age as these children constitute the majority affected by the disease. As demonstrated by comparison to other reports they differ from those who are older. Interesting questions are raised regarding the aetiology of acute infectious infantile diarrhoea and avenues for further research in this area are identified. Of particular importance are the factors resulting in the characteristic summer peak in the disease and the demonstration of variable pathogenicity of micro-organisms associated with acute diarrhoea. Other numerically important aetiological agents (most likely viral) almost certainly remain to be identified. These together with the effects of general bacterial overgrowth of the small

bowel are probable factors resulting in much of the summer peak of disease so typical of many areas of the developing world.

The deleterious effects of acute diarrhoea in young well-nourished infants are demonstrated by the results of this study. Prevention of the disease would be the ideal but reduction of the morbidity associated with acute infectious diarrhoea is a more realistic immediate goal. Since the completion of this study a home and community based oral rehydration program has been successfully commenced in the Crossroads area from which most of the Black patients originated. This was a recommendation originating from the findings.

In conclusion it may be said that the findings of this study define and clarify acute infectious infantile diarrhoea as seen in infants under one year in Cape Town. This information serves as a baseline for further research and recommendations as to prevention and effective management of the disease.

ADDENDUM

Subsequent to the preparation of this thesis certain important developments have taken place. These are reviewed here and where appropriate the addendum is referred to in the main text.

Aetiological agents:

Many viruses have been detected in diarrhoea stools through electron microscopy but their role as significant aetiological agents remains to be determined. A major problem in the study of these viruses has been the inability to cultivate them in tissue cultures. This problem has been overcome with rotavirus[228].

Enterohaemorrhagic Escherichia coli is a new class of Escherichia coli recently described. The organism produces a potent cytotoxin identical to the Shiga toxin[219,186] and the genes coding for the production of this toxin are contained in bacteriophages[220]. Infection is characterised by crampy abdominal pain and initially watery diarrhoea which later becomes grossly bloody. Colitis is evident on sigmoidoscopy and on barium enema[114,186]. Diagnosis is by serotyping and should be done early in the course of the illness as the organism disappears from the stool within 5 to 7 days. No specific treatment is recommended at present.

Aeromonas hydrophilia is a member of the genus Vibrionaceae and has been reported in association with diarrhoea in children[174,188]. Diarrhoea usually lasts less than a week but may become protracted. The organism grows well on standard non-selective media such as Salmonella - Shigella

and Mac-Conkey agar, however, a specific oxidase test must be performed to differentiate it from the Enterobacteriaceae. The organism is sensitive to cotrimoxazole but the necessity for treatment is dubious.

Plesiomonas shigelloides is another organism linked with diarrhoeal disease[234,168] but its significance remains uncertain. Gracey[189] reports that he has searched unsuccessfully for this organism in children with acute diarrhoea for several years.

Cryptosporidium another recently described enteropathogen is discussed fully in the main text of the thesis (p 166-167). Further published studies indicate that Cryptosporidium accounts for 4 to 10 percent of acute infantile diarrhoea[238,229] and that the incidence may be even higher during the wet rainy season[208].

Pal et al[221] recently have described an enzyme-linked immunosorbent assay (Elisa) suitable for testing large numbers of isolates for entero invasive E.coli and virulent Shigella strains. The development of this type of screening test will enable laboratories in developing countries to elucidate the aetiology of infectious infantile diarrhoea more fully.

Pathogenesis:

A particularly significant breakthrough has occurred in the understanding of pathogenic mechanisms of enteropathogenic E.coli[175]. Ultrastructural examination of intestinal biopsies of animal models[176,213] and ill infants[224,235,199] has revealed a distinct histopathological lesion. The enteropathogenic E.coli (EPEC) adhere intimately to the enterocytes of the small bowel with resultant

dissolution of microvilli, cupping of the enterocyte outer membrane around the bacterium and round cell inflammatory infiltrate in the lamina propria. All EPEC tested thus far produce this typical lesion[213,180].

Entero-adhesion is a property present in 80 percent of classic EPEC serotypes in vitro while it is uncommon in other strains of E.coli[178]. Human epithelial cell (HE_p-2) adhesiveness and the ability to adhere to intestinal mucosa is coded for by genes on a 60 MDa plasmid[239]. The term EPEC adherence factor (EAF) has been suggested for this plasmid mediated adhesion[169]. A DNA hybridisation probe has been shown to be highly sensitive and specific in detecting EPEC strains that exhibit HE_p-2 adhesiveness[170]. Field trials have shown that EAF is more frequent amongst EPEC O serotypes causing epidemic diarrhoea (Class I: 055, 0111, 0119, 0127, 0128, 0142) than other types (Class II: 044, 086, 0114)[217,201]. EPEC lacking EAF (Class II) may also produce diarrhoea by mechanisms not utilising HE_p-2 adhesiveness[204].

Toxin production by EPEC also may play a role in the pathogenesis of diarrhoea. A local cytotoxin may result in epithelial cell damage[225]. Certain EPEC serotypes elaborate a Shigella-type enterotoxin but its role in diarrhoeal disease remains uncertain[180,218].

A recent report[241] suggests that the ability to assimilate iron may determine virulence of enteropathogenic E.coli. EPEC producing a siderophore, aerobactin, enabling effective iron uptake were more frequently isolated from classical EPEC serotypes associated with diarrhoeal disease. Ferric-aerobactin seems to confer a selective advantage for bacterial growth in tissue and body fluids[240].

Enterotoxigenic and invasive E.coli were not assessed in the present study and advances made in this area will not be reviewed in detail. The mechanisms whereby the toxins (LT and ST) produce diarrhoea have been further clarified. The genes coding for their production and the genes coding for colonisation and virulence factors have been found on plasmids[231]. These plasmids may be transferred from one strain to another producing enterotoxigenicity in the recipient. Radiolabelled probes for these genes allow rapid detection of enterotoxigenic strains without the need for culture and bioassay[214]. This has important implications for future epidemiological surveys such as the one on which this thesis is based.

The pathogenic mechanism of Campylobacter remains uncertain. Recent work[202] suggests that mucus colonisation may be a major determinant of pathogenicity in intestinal infection with Campylobacter. In another study[198] Campylobacter isolated from asymptomatic carriers failed to produce enterotoxin, had no cytotoxic effect in Vero and Hela cells and resulted in no fluid secretion in rat ligated ileal loops. In contrast strains from persons with invasive-type bloody diarrhoea produced enterotoxin and low titre cytotoxin. Strains resulting in secretory-type diarrhoea produced varied quantities of enterotoxin but all evoked fluid secretion in rat ligated ileal loops. Other work[196,209] has confirmed the production of heat-labile enterotoxin by some strains. This work suggests varied pathogenic mechanisms by which Campylobacter causes diarrhoeal disease.

The precise pathogenic role of Shigella toxin remains unclear. It appears that the properties of invasiveness and intracellular multiplication are located on both the bacterial chromosome[183] and a

large plasmid[227]. The mechanism whereby Salmonellae cause intestinal secretion remains unclear. Apparently both mucosal invasion and enterotoxin production are necessary[187].

Vaccines:

Much effort has been concentrated in recent years on the development of vaccines for the prevention of acute infectious infantile diarrhoea. It is important to remember that the appropriate use of vaccines requires detailed epidemiological information from areas of high incidence. This information is lacking in many areas.

The development of vaccines against rotavirus has been hampered by the inability to culture the human rotavirus. This has been partially overcome[228]. Many possible avenues of research have been considered.

Firstly attenuated animal rotaviruses have been used successfully as human vaccines. Bovine rotavirus strain RIT 4237 produced 60 to 80 percent seroconversion and 88 percent protection of infants against rotavirus diarrhoea over one diarrhoeal season[236]. The vaccine was more effective administered with milk feeds to protect the acid labile attenuated rotavirus[237]. Other animal rotavirus strains such as bovine rotavirus WC3[177] and rhesus rotavirus vaccine strain MMU 18008[206] have also produced encouraging results and further clinical trials are envisaged.

Secondly the attenuation of human rotavirus by repeated passage in tissue culture has been attempted. A limited study[197] in which human rotavirus was passed through gnotobiotic piglets and then African green

monkey kidney cells resulted in seroconversion and no side effects in adult volunteers. Further studies are required to evaluate this vaccine.

Another possible avenue for research is the cloning of a DNA copy of the RNA genes responsible for the neutralising antigens of rotavirus into a bacterium. This bacterium (for example S.typhi Ty 21a see below) could express the antigen in vivo and thereby stimulate an immune response. It also has been proposed that from a synthetic peptide of the critical epitope of the neutralisation antigen, purified antigen could be prepared. Another possibility is the hybrid reassortant strains that could be produced by coinfecting tissue cultures with both animal and human strains. A hybrid virus could result which possesses the human virus neutralisation antigen and grows readily in tissue culture. These possibilities which have been reviewed recently in an article by Levine et al[205] present the very exciting possibility of control of rotavirus diarrhoea within the forseeable future.

Enteropathogenic E.coli of Class I as mentioned earlier contain plasmids coding for EAF. The possibility thus exists for the development of vaccines for use against the EPEC group. Development of such vaccine undoubtedly will have a great impact on diarrhoeal disease in the developing world.

Killed parenteral vaccines consisting of whole Shigella organisms have proved ineffective[190] but attenuated Shigella strains used as oral vaccines have proved effective[211]. A recent development is a bivalent live attenuated vaccine strain of Salmonella typhi and Shigella sonnei[184]. A 120 MDa plasmid from Shigella sonnei containing genes

encoding for the O antigen was transferred into an attenuated S.typhi vaccine strain Ty 21a. The resultant hybrid S.typhi 5076-1C produces both S.typhi and Sh.sonnei O antigens and has been shown to be effective in volunteers. Other hybrids (E.coli K2 - Shigella flexneri 2a) have been developed[185] and field trials are awaited.

Oral Rehydration:

Oral rehydration has been accepted in the last decade as an inexpensive, appropriate and effective form of therapy for mild to even severe dehydration[203h230]. A new development is the so-called 'Super Solution' described initially by Nalin et al[216] and recently reported in infants with acute diarrhoeal disease and dehydration[223]. The presence of more than one actively absorbed substrate (such as glucose and glycine) results in reduced stool volumes and shorter duration of diarrhoea. Rice powder/electrolyte solution has been shown in some studies to be superior to the standard glucose electrolyte solution[222,210,212]. Rice contains significant amounts of glycine. In addition the oligosaccharides in rice powder when substituted for glucose in the standard solution facilitate the slow release of small carbohydrate molecules for digestion and absorption[212]. These developments may enable the nutritional insult of the acute diarrhoeal episode to be reduced further.

Another interesting development is the suggestion that tripotassium citrate should replace sodium bicarbonate (or sodium citrate) and potassium chloride. Such a product was shown to be effective in treating dehydration and none of the 94 children in this trial developed

hyperkalaemia[194]. It is suggested that this product may be beneficial in developing countries where diarrhoea, malnutrition and hypokalaemia are interlinked.

JULY 1986

ANNEXURE A : CHAPTER 3

QUESTIONNAIRE USED TO ELICIT AND RECORD PATIENT DATA

EXAMPLE: PATIENT NUMBER 5

A9 DIARRHOEAL DISEASE SURVEY

Name: Samara Kobus Hospital No. 59 168 427 Survey No. 5

Date of Birth: ..... S KOBUS SANDRA

Date of Admission : 2.4.91 (10/12) 59168 427

Date of Discharge : ..... BORN: 30/05/1980 R/S: 4

Sex: M (F) Bantu.

History: Diarrhoea 4 days. Stools 11 No/day. Static/Progressive/Intermitter

Consistency: Watery / Loose / Formed. Blood / Mucus / Worms

Vomiting: 1 days. Static/Progressive/Intermittent

Previous treatment for diarrhoea: D.H. / G.P. / Trad. / Home

Systematic interrogation: Cough: Yes / No. Fever: Yes / No. Convulsions: Yes / No.

Other complaints: .....

Basic History: Birth: NVD Birth Weight: 3kgs Place: Home

Perinatal Problems: Well.

Feeds: Breast: (duration) 21/52 Solids: Cereal / mealie meal / eggs

Bottle: Milk Lactogen Strength: 1 scoop Amount: 1 cup 250

Social History: Mother: Age: 24 Education: Matric + nurse Married: Yes / No

Father: Age: 30's Employment: Shop owner

Siblings: (number) 0 Family Income: Supports Rands

Current Address: (area only) Eyethu Housing: House

Usual residence: Ram C1 Emvuzo

Examination: Weight on admission: 7kg 960 gm Weight on discharge: 8,04 kg

Dehydration: 5% (.....%tile)

Nutrition: Normal / Underweight / Kwashiorkor / Marasmic / M-K

Skin: Skin sepsis Carbuncle forearm Mucous membranes: Moist

Ears: L. ✓ Right ✓ Nose (N) Throat: Red Inner tonsils

CVS: Pulse: 140 /min. BP: (N) / .... HS. Normal.

RS: Rate: 35 /min. Clinical Acidosis: Yes / (No)

Chest: Clear

Abdomen: Liver: 1cm (N) Spleen: 0

Bowel sounds: ↑ Genitalia: ♀ (N).

CNS: LOC Fully conscious Meningism: Nil

Fontanelle ←→ Cranial nerves: Normal.

Limbs: Upper. Lower.

Tone:

Movement: Normal.

Reflexes:

Other: ....

Course	Weight	I.V. therapy	Feeds	Medication	Clinical Features
Day 1	7960	1/200 I.V. INPM	→ 0 Smaw Fu milk feeds	[illegible]	–
36.2°C 2	8020	I.V. 1/200	Fu 80 x 8	→ Fu 150 x 8 [illegible]	
3	8080	[illegible] I.V. 1/200	Fu 150x8	Various [illegible]	D/c 16.30 4.4.81. 7.04
4					
5					
6					
7					
8					

Outcome / Summary: Duration of stay: 3 days.

Disposal: Ward / (D.H.) / Other hospital / Home / Died

Antibiotics: Yes / (No.) if yes Oral / I.V.

Associated illness: (Yes) / No. if yes - Type: Skin [illegible] - [illegible] no Rx.

Significant clinical features: (RELAPSE) <1/52 5.4.82 - 7.4.82 150 7[illegible] x 1/52.

Diarrhoea again 24.3.82 - 25.3.82

Name: Sarah Kobus

Survey No. 54163427

Investigations General data

Date	6.4.81				Comment
pH	7.16				
pCO_2	26				
BE	-18.4				
SB	10,1				
Na^+	142				
K^+	3,5				
Ca^{++}	2,49 / 1,19				
Urea					
TPA					
Hb	11.9				
WBC	10.00				
MCV	82				
MCHC	34				
Diff	67/29/3/1 → ⊖				PROTEINS: 76 : 44,3
Urine Micro	/ Negativ				
Culture	/				
Blood culture	6.4.81. N/G.				
CXR					
Others					

ANNEXURE B - CHAPTER 3

Method and Media used in culture of Campylobacter species.

Children's Hospital Burchell B, Roux E.

Stool is initially plated onto Tryptose Blood Agar Base plus Antibiotics (TBAA plates) TBAA medium is based on "Skirrows medium"[141].

Constituents :	Tryptose	)	
	Lab-Lemco Powder	)	commercially prepared
	Sodium chloride	)	medium by Oxoid. (TBA)
	Agar No 3	)	
Antibiotics :	Vancomycin	)	
	Polymyxin	)	commercially prepared
	Trimethoprin	)	supplement by Oxoid. (A)

Plus 250 ml sheep's blood per 500 ml Agar.

TBAA plates are incubated under microaerophilic (carbon dioxide) conditions for 2 to 3 days. Suspicious colonies are picked off and a gram stain performed. Subculture of positive cultures is then done on TBA plates (i.e. Medium without the antibiotics and sheeps blood 50 ml per 800 ml Agar).

ANNEXURE C : CHAPTER 3

Viral transport medium:

Constituents :

Hanks solution A	250 ml
Hanks solution B	250 ml

Base :	Glucose	5 g
	Lactalbumin hydrolysate	25 g
	Distilled water	2 500 ml

No added sodium bicarbonate or antibiotics

Filter by pressure filtration and store at -20°C or 4°C

Preparation of transport medium for use.

Transport medium base	100 ml
10% Bovine plasma albumin	5 ml
5% sodium bicarbonate	0,7 ml
1N sodium hydroxide	0,3 ml to correct pH

Incubate overnight at 37°C to exclude bacterial contamination and store thereafter at 4°C.

Hanks solution A

NaCl	320 g	
KCL	16 g	in 2 litres of distilled water; filter and store at room temperature
$MgSO_4$. 7H20	8 g	
CaC12	5,6 g	

Hanks solution B

Na_2HPO_4	2,4 g	
KH_2PO_4	2,4 g	
Glucose	40 g	Above diluted in 800 ml distilled water plus 200 ml 0.4% Phenol red and make up to 2 000 ml. Filter and store at room temperature.

ANNEXURE D : CHAPTER 5

STANDARD FLUID THERAPY

	FLUID	VOLUME	ROUTE	RATE
Resuscitation (shock)	Plasma volume expander	20 ml/kg	I.V.*	Rapid
	Sodium bicarbonate 8,5%	2 mmol/klg	I.V.	Rapid
Replacement	Half-strength Darrow's solution in 5% dextrose	5% dehydration 50 ml/kg	I.V.	Constant rate over 24 hours
		10% dehydration 100 ml/kg	I.V.	
Maintenance	Half-strength Darrow's solution in 5% dextrose	1 yr: 120 ml/kg/day	I.V. or Oral	
Ongoing loss	Half-strength Darrow's solution in 5% dextrose	50-200 ml+/stool	I.V. or Oral	

* I.V. = Intravenous

\+ Calculated after initial period of observation and requires frequent reassessment

ANNEXURE E : CHAPTER 5

CLINICAL CRITERIA FOR THE ESTIMATION OF DEHYDRATION

DEGREE OF DEHYDRATION (% body weight lost)	CLINICAL STATE	CLIINCAL SIGNS
5% (Borderline)	Not unwell + Significant diarrhoea	Thirst Skin turgor normal + − Dry mucous membrane
5%	Often apathetic	Reduced skin turgor (pinch retraction slow) Often sunken eyes
10%	Apathetic Unwell	Markedly reduced skin turgor (pinched retraction very slow) Sunken eyes Sunken fontanelle Tachypnoea Oliguria
15%	Poor circulation (shocked)	Markedly reduced skin turgor Sunken eyes Sunken fontanelle Hypotension Poor peripheral circulation (vase constriction) Tachycardia

Note: At times patients were felt to lie between values given above. This was particularly so between 5 and 10% and these patients were recorded as 7,5% (see Table 5.2).

ANNEXURE F - CHAPTER 6

THREE ORGANISMS

ORGANISMS	PATIENT GROUP n = 545		CONTROL GROUP n = 297	
	[1]All Isolates Patients	*Significant Isolates Patients	[1]All isolates Controls	*Significant Isolates Controls
Rotavirus Campylobacter and EPEC	3	3	3	1
Rotavirus and EPEC (2 types)	2	0	0	0
Rotavirus Campylobacter and Salmonella	1	0	0	0
Rotavirus Campylobacter and Shigella	0	2	0	0
Rotavirus EPEC and Salmonalla	1	0	0	0
Rotavirus EPEC and Shigella	1	0	0	0
Campylobacter and EPEC (2 types)	1	0	1	0
Campylobacter EPEC and Salmonella	5	0	2	0
Campylobacter EPEC and Shigella	3	1	0	0
Salmonella and EPEC (2 types)	1	0	0	0
EPEC (3 types)	0	0	1	0
TOTAL (percentage)	18 (3,3%)	6 (1,1%)	7 (2,4%)	1 (0,3%)

1 Includes ALL organisms identified in the stool specimens
* Includes only those organisms found to be 'significantly' associated with diarrhoea: Rotavirus, Campylobacter fetus jejuni, EPEC types B16, B14 and B8, Salmonella type B, Shigella types A and D and Yersinia enterocolitica.

FOUR ORGANISMS

	PATIENT GROUP n = 545		CONTROL GOUP n = 297	
	[1]All Isolates Patients	[*]Significant Isolates Patients	[1]All Isolates Controls	[*]Significant Isolates Controls
Rotavirus and EPEC (3 types)	1	0	0	0
Salmonella and EPEC (3 types)	0	0	1	0
Rotavirus, Campylobacter EPEC and Shigella	1	0	0	0
Rotavirus, Campylobacter Salmonella and Shigella	1	0	0	0
TOTAL (percentages)	3 (0,5%)	0	1 (0,4%)	0

1 Includes ALL organisms identified in the stool specimens
* Includes only those organisms found to be 'significantly' associated with diarrhoea: Rotavirus, Campylobacter fetus jejuni, EPEC types B16, B14 and B8, Salmonella type B, Shigella types A and D and Yersinia enterocolitica.

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