STUDIES ON INFANTILE DIARRHOEA WITH SPECIAL REFERENCE TO THE WATER AND CHLORIDE METABOLISM.

By

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PART I.

SECTION A - Historical Introduction.

SECTION B - A Clinical Analysis of the Case Records of 300 Patients.

PART I. SECTION A.

(A). Historical Introduction and Classification.

It is definitely with fear and trepidation that I now attempt an incursion into the lanes and byeways of present day thought, understanding and classification of that common complaint of infancy known to some as diarrhoea and vomiting, to others as summer diarrhoea and to still others by a multitude of different names amongst which may be mentioned gastro-enteritis, atrophy with dyspepsia (Parsons)[1], cholera infantum, anhydremia (Marriott)[2] and alimentary toxicosis (Czerny)[3]. It will thus be seen that even at the present stage of our knowledge there still exists much confusion in the classification of the gastro-intestinal troubles as they occur in infancy.

In this section of the paper only a brief résumé will be given of the most important contributions by various well-known authors to this vexed condition.

Since the beginning of the present century a large amount of research work has been carried out in nutritional disorders as they affect infancy. To Czerny[3] belongs the credit of emphasizing the importance of the consideration of the child as a biological unit and not focussing one's attention only on the alimentary tract or the diet. He also deserves mention for the fact that it was he who demonstrated that the protein of the milk was in itself harmless in these conditions.

Czerny[3] classified the nutritional disorders under three main headings:-

(A). ex alimentatione - food disturbances

(a) Milchnahrschadin - due to fats.

(b) Mehlnahrschadin - due to carbohydrate.

(B). ex infectione (a) enteral

(b) parenteral

(c) acute disturbances.

(C). ex constitutione - rickets, anaemia and congenital malformations.

According to present day standards most of the cases met with fall under the first two headings (A and B). Karelitz[6] indeed believes that most cases belong to group (B), holding the view that practically all the conditions attributed to faults in feeding are in reality due to bacterial infection. Czerny[7] himself, lays great stress on the constitutional factor as a cause of wasting and atrophy in many of these infants. He says "Before going deeper into the subject I should like to put the question before you, whether under like conditions every nursing infant becomes atrophic or whether to do so is the tendency of only certain ones. I should like to answer this question by saying that the occurrence of atrophy irrespective of the cause producing it, is directly the result of constitutional anomaly. We are all aware that the same errors are made in feeding many children yet only a proportion of these become atrophic."

Finkelstein[4] used a different basis for his classification which represents stages in the development of alimentary disorders: a simple dystrophy may continue to represent this stage of the disturbance for a considerable time or it may gradually pass into the next stage - dyspeptic dystrophy. The whole group of nutritional disorders should be regarded as a gradual development of an increasing intolerance for food.

(A). Alimentary Disturbance
- (a) Dystrophy
  - (1) Simple without diarrhoea.
  - (2) Dyspeptic form with diarrhoea.
- (b) Decomposition (Rapidly progressing emaciation).

(B). Toxicosis
- (a) Mild (acute dyspepsia)
- (b) Severe form.

While Czerny[3][7] was inclined to stress the important part played by the fat of the diet (Milchnährschaden) in the production of disorders of nutrition, Finkelstein[4] emphasized the importance of the whey with its sugars and salts as the causative factor. Probably both factors play some part in the causation and continuation of the vomiting and diarrhoea once this has been initiated.

In contra distinction to the work of the Germans, the French pediatricians attempted a classification under the symptomatology of the disease and divided the condition into two main groups.

(a) mild form - acute dyspepsia or catarrh

(b) severe form - acute gastro enteritis (Abt)[9]

More recently the work of several American pediatricians has attracted attention to the condition of "alimentary disturbance". Thus Marriott[2] divides these conditions into acute and chronic disturbances, the acute including diarrhoea and what he calls "anhydremia" and the chronic "hypothrepsia" and "athrepsia". He[2] has also taken great pains to stress the importance of the buffer action of cow's milk in the production of nutritional disorders. This increased buffer action of cow's milk prevents the infant's stomach producing sufficient hydrochloric acid for optimum digestion and also allows an increased number of organisms to remain in the milk, which are liable to set up alimentary disturbances further down the gastro-intestinal tract.

In recent years, there has been an attempt and tendency in this country to simplify the classification of atrophy and its allied nutritional disturbances and Parsons[1] of Birmingham has suggested the following:-

(A) Simple atrophy.

(B) Atrophy with dyspepsia

(a) diarrhoea and vomiting.

(b) due to fat dyspepsia.

(c) due to carbohydrate dyspepsia.

(C) Atrophy from deprivation.

(D) Atrophy due to infection.

(B). Aetiology.

In considering the cause of infantile diarrhoea and vomiting one is struck by the large numbers of aetiological factors which have been suggested by different observers at various times. It is also amusing to note that certain conditions such as allergy and avitaminosis, fashionable at one time or another, have each been suggested as the possible cause of alimentary disturbances in infants.

It has long been noted that this condition of vomiting and diarrhoea is more prevalent in the hot summer months, hence the name "summer diarrhoea". Within the past few years however, larger numbers of cases have occured during the winter months.[(10)] As a result of the summer incidence many and varied were the explanations offered, amongst which may be mentioned humidity. It was believed that when the humidity rose above a certain level the infants became more liable to an attack of diarrhoea and vomiting. It should however he noted that infantile diarrhoea is a disease almost exclusively associated with artificially fed infants[(12)], and no doubt the correct explanation why more cases are affected during the warmer months of the year is that either milk is more liable to become fermented during this period, or else infection is carried to it by flies which are very prevalent during these months.

Constituents of Milk.

It has previously been mentioned that Czerny[3] emphasized the fat in milk (Milchnahrschaden) as well as the sugar (Mehlnahrschadin) as two of the main factors in the production of alimentary derangement, while Finkelstein[4] was inclined to lay more stress on the whey and its constituents as the causative factor. Marriott 1919[13] would not subscribe to the view at first that the fat of the diet played any part in initiating these alimentary disturbances, but in a later publication (14), (15) he states that in these cases of alimentary derangement the fat content of the milk should be reduced during the treatment of these cases.

It is also a well-known fact that children suffering from any condition which results in some degree of malnutrition, are very liable at any time to develop an alimentary derangement. It is often noticed that after a severe winter many children, particularly those of the poorer classes, are undernourished. It is thus not surprising that many of them develop infantile diarrhoea and vomiting during the warm summer months as a result of overfeeding on a diet too rich in fat and carbohydrate. Czerny[10] has maintained the attitude that alimentary toxicosis will disappear or be met with only seldom if the children enter the summer season in a healthy state or when nutritional changes in children are immediately treated and not left until they are in a serious condition.

Specific Intestinal Infections.

With reference to specific infections (typhoid, dysentry), as a cause of infantile diarrhoea and vomiting, very few patients in this country have these conditions. Nabarro[16] discovered only 17 cases of dysentry in a series of 104 examined by him.

Zahorsky[17] in an examination of 85 patients suffering from diarrhoea came to the conclusion that summer diarrhoea is an infectious enteritis as he was able to detect pus in the stools of most of the cases. It should be noted however that none of the stools in this series were cultured. According to the American publications however about 40% of all their cases fall into the class of specific intestinal infections. Marriott et alii[15] in a review of 318 cases at St Louis, over a three year period discovered that 37% of these were due to specific infections. Rather similar findings are published by Wilkins[18] of Baltimore, while Johnston et alii[19] in a series of 170 patients under the age of 2 years discovered that 67% yielded on stool culture, pathogenic organisms of the coli-dysentry group. In contrast to these findings, Day and Gerstley[20], in a small series of 22 cases, discovered very few infants suffering from a specific intestinal infection and state that in the Middle West fewer cases of infantile diarrhoea are due to definite specific infections than is the case on the Eastern borders of the United States. They suggest that these findings in the Middle West are due to the fact that all milk is boiled, whereas raw milk is used for infant feeding in the Eastern states.

Nevertheless although a specific intestinal infection is not often discovered amongst cases of infantile diarrhoea and vomiting in this country, it is always advisable, especially during the warm summer months, to be on the alert for the presence of this type of the disease.

Parenteral Infection.

It has long been well recognised that, as the result of any parenteral infection, young infants are liable to develop all the signs and symptoms of an alimentary tract disturbance. It should be remembered that in infants the alimentary tract may be likened to the "bell of an alarm clock", just as in adults and older children another "bell" - pain, headache - is often the first indication that more serious symptoms are to follow. It is thus quite evident that an alimentary derangement may be initiated in infants by a disease process acting in some other part of the body and not primarily related to the gastro-intestinal tract.

Both Hartmann[21] and Findlay[12] have stressed the importance of middle ear infections as the primary aetiological factor in many of these cases of diarrhoea and vomiting. Maizels and Smith[22] have demonstrated in their series that 60% of the post mortem material exhibited some degree of infection in the middle ears but offered no suggestion, as to whether this was the primary aetiological factor or whether it developed during the course of the diarrhoea and vomiting. On the other hand Nabarro[16], in a paper published in 1923, considers that the disease is one and the same the world over and is not an infections disease in the strict sense of the term, but rather of metabolic origin with secondary infection by one of a number of different micro-organisms.

In another series of cases examined by Marriott et alii[15] it was discovered that 83% of the cases were suffering from some parenteral infection on admission. Karelitz[6], in a series of 71 cases, demonstrated that half of them were due to some parenteral infection. Jeans and Floyd[23] however are of the opinion that nearly every case of acute gastro-enteritis suffers from some type of upper respiratory infection, which may not be obvious during the course of the diarrhoea and vomiting.

Most clinicians will agree that many patients brought to hospital with the complaint of diarrhoea and vomiting turn out on later examination to be suffering from some parenteral infection. It is however exceedingly difficult if not at times impossible to detect any parenteral infection at the time of admission although after a few days' sojourn in the wards, definite evidence of middle ear, nasal sinus, pulmonary or urinary infections is often obtained. The great difficulty is to decide whether or not the parenteral infection is the predisposing cause of the alimentary upset. While in some cases this is true, it is probable that in others, otitis media, which is so common in these cases results from vomited material passing into the relatively patent and large Eustachian tube and thus develops after the onset of the alimentary symptoms. With reference to renal tract infections, which are more often encountered in cases with chronic infantile diarrhoea, it is likely that these develop quite frequently as the result of (a) diminished resistance of the infant, (b) diminished urinary excretion, states so frequently met with in these cases of infantile diarrhoea and vomiting.

From all that has been said there can be no doubt that parenteral infections play an important part in the causation and perhaps continuation of infantile diarrhoea and vomiting.

<u>Various other theories.</u>

It might be mentioned here that Abt[9] has credited spoilt milk as a cause of infantile diarrhoea, his view being that with the formation of peptones and fatty acids in the milk the intestinal mucosa of the bowel becomes irritated and there results increased peristalsis and loose stools. At one time or another different investigators have suggested various other factors as the cause of infantile diarrhoea. Thus Mellanby[24] has suggested that in the severe cases the cause was a histamine-like product, produced probably in the alimentary canal as the result of amino acid break-down. He discovered that on injecting this substance, called by him B-imidazolyl-ethylamine (Histamine), into the cat the following symptoms could be elicited:-

Diarrhoea and vomiting, fall of blood pressure, depression of the respiratory centre and coma. These appear to be symptoms rather similar to those found in infants suffering from severe and acute infantile diarrhoea. He also noted that the effect of this drug appeared to be more marked if the animal had previously been deprived of food and water and put forward the view that the hot weather results in a diminution of body fluid by evaporation in infants, so that when an ordinary digestive derangement occurs the further loss of fluid permits the action (of histamine) to exert its maximum deleterious effect. In cats he found that by injecting fluid into the circulation the absorption of B-imidazolyl-ethylamine was diminished and the toxid effect greatly lessened. On the other hand Ruben and Kellett[(25)] discovered that dehydration in guinea pigs protected them from lethal histamine shock - suggesting that the reason why chronic cases do not die is that as the result of dehydration the action of histamine is not at its maximum.

It appears quite probable that in the severe and acute cases of infantile diarrhoea some product of amino acid breakdown, ? histamine, plays an important part in the production of such symptoms as toxecity and shock, particularly as these signs and symptoms appear so soon after the development of the diarrhoea and vomiting.

On the other hand Marfan[(26)] has blamed a specific micro-organisms in the milk as the causative factor in the production of infantile diarrhoea, while Schloss and Worthen[(27)] and Schloss[(28)]

have been imbued with the idea that infantile diarrhoea is an allergic phenomenon and suggest that there is something present in raw milk which is able to produce this condition. They believe that if the milk is properly boiled infants do not develop the condition, but that with the addition of a minimal quantity of raw milk to the boiled portion alimentary disturbances were likely to occur. It should be noticed however that no reaction results in these infants when the milk is injected subcutaneously.

Marriott, Hartmann and Senn[15] found that the gastric juice of infants with a non-specific diarrhoea showed a diminished acid content and that in these cases 45 per cent. gave a bacillus coli growth on culture. They suggested that infantile diarrhoea might be due to this diminished acid content of the gastric juice. Arnold[29] also seems to share their views, that as a result of diminished acidity in the stomach, due he thinks to an elevation of atmospheric temperature, the result of summer heat, bacteria are allowed to grow and flourish in a portion of the intestinal tract where they are not usually found and thus produce enteritis.

More recently, as the result of the prominence given to vitamins as the cause of many diseases, many cases suffering from alimentary disturbances have been credited with a lack or absence of essential vitamins in their diet.[16] Several of the German pediatricians[30][30a] are inclined to this view of avitaminosis and, as a result, there exists in that country the vogue for feeding and treating cases with large quantities of grated raw apple. Marriott[14] also maintains that vitamins are essential for the infants' recovery.

(C). Distribution.

It is of interest and importance to note that in this country most of the cases of infantile diarrhoea occurring in young children have a somewhat similar distribution to that of rheumatism. It is usually encountered in those patients inhabiting the slums of large cities and is seldom seen in the better classes of the community.(1)(12) It is also remarkable to observe that, during an average summer in a large industrial English city like Coventry, very few cases of infantile diarrhoea are admitted to the medical wards of a large voluntary hospital (personal experience of writer). Probably this observation can be explained by the fact that Coventry, although an industrial city, is fairly modern, supporting few slums and that the population, generally of a higher intellectual class, understand fully the words "purity and cleanliness," so far as these apply to their own and their children's diet.

From what has previously been stated it will be quite evident that it is absolutely impossible to designate any one aetiological basis for the nutritional and alimentary disturbance of infants, and it should be remembered that this "disease," if such it may be called, must be approached with an open mind and with the knowledge that a large number of factors probably play a part in its development. There is no doubt that at present, whatever the cause, epidemics of infantile diarrhoea are not as prevalent as they used to be. This is most probably due to the many public health restrictions in relationship to the water and milk supply as well as the increased use of dried milks in contemporary infant feeding.

(D). Age Incidence.

For clarity it may be stated here that "infancy" is taken to cover the period from birth to two years of age. Most attacks of infantile diarrhoea appear to occur during the first year of life. This finding is probably due to the fact that at this age the normal alimentary mechanism is very easily upset by trifling indiscretions in diet and mild infections, factors which would have little or no effect on older children. According to Wilkins[18] of Baltimore, however, cases with nutritional and intestinal disorders occur more often in the second than in the first summer of a child's life. This he suggests is due to the fact that most cases are breast fed during the first summer, but are often weaned or artificially fed during the following summer. It is the general opinion of paediatricians in this country that if a child can be successfully reared until after the age of one year, there is not much likelihood of infantile diarrhoea proving more than mild in character and easily amenable to efficient treatment.

(E). Symptomatology.

The signs and symptoms depend to a great extent on whether the acute cases of infantile diarrhoea or the chronic cases are being described.

In considering first those suffering from acute infantile diarrhoea, it is usually found that there is often only a very short history of previous alimentary disturbance. The child suddenly sickens and commences to vomit everything given by mouth. This is followed almost immediately by profuse dark green, slimy or watery diarrhoea which often has a very foul odour. The infant, on admission to hospital, usually exhibits all the signs of shock and toxicity - ashen grey colour, cold extremities, feeble rapid pulse, subnormal temperature and rapid deep respirations. Usually within a very short time definite evidence of dehydration occurs, manifested by the loss of skin turgor, sunken fontanelle and hollowness round the eyes. The children are often restless, tossing from side to side, and a fairly constant finding is the presence of anuria.[31][38]

To Czerny[5] belongs the credit of first suggesting that the cause of the increased respiratory rate was a condition of acidosis: he noticed in dogs a similar condition after they had been poisoned with organic acids. This observation of Czerny's was experimentally proved by the work of Howland and Marriott,[31] Schloss and Stetson[32] et alii[33], the former investigators discovering a diminution of the alkali reserve of the blood in cases of acute infantile diarrhoea. According to Holt, Courtney and Fales 1915,[34] there occurs an excessive loss of

<u>fixed base</u> from the body in patients suffering from severe
fixed acid
diarrhoea. This finding would suggest that the cause of the acidosis is most likely due to the greater loss of fixed base. Howland and Marriott,[31] and later Holt[35] et alii[38], however, have suggested that the acidosis is more probably due to a diminished output of inorganic phosphate and acid ions by the

kidney, while Schoenthal, Lurie and Kelly[39] believe that the acidosis is due to a decreased oxygenation of the renal tissue as well as other body tissues, with resultant accumulation of acids in the body.

The grey colour and coldness of the extremities have been demonstrated by Utheim[36] and Marriott[14] to be due to a diminished volume flow of blood in the superficial capillaries of the body. This diminished volume flow is probably due either to an increased specific gravity of the blood, the result of fluid loss, or perhaps to some degree of cardiac muscle weakness - McCulloch[37] having demonstrated some abnormality in certain of the electrocardiographic tracings of dehydrated infants, which he suggests are due to a deficient oxygen content of the coronary artery blood.

The other important symptom which has attracted attention is that of anuria. Schloss,[38] as far back as 1918, was able to demonstrate that these infants showed a marked degree of renal insufficiency, definitely not due to organic lesions in the kidneys themselves, but due to the negative water balance, the result of excessive water and salt loss by the alimentary tract. His findings have been confirmed by the Work of Schoenthal, Lurie and Kelly[39] on the urea clearance in dehydrated infants.

This symptom and that of dehydration, which are so closely related, are of the greatest importance in patients suffering from infantile diarrhoea, for they require energetic and prolonged treatment, which, if promptly applied, not infrequently results in clinical improvement.

So far as chronic diarrhoea and vomiting is concerned the infants are usually undernourished, showing variable signs of dehydration and often marked emaciation. They are often well under their expected weight, but do not usually exhibit any clinical evidence of acidosis, although they very often have varying degrees of coldness and blueness of the extremities [14] There is often a diminished excretion of urine but never to the same extent as is found in those suffering from acute infantile diarrhoea. These patients with chronic diarrhoea are usually difficult to treat, shewing improvement for short periods with a change of diet, only to relapse again into their former poor state, until pneumonia or some urinary tract infection closes the scene. It should be remembered however that these chronic cases are liable to develop an acute exacerbation of their condition, when they will exhibit all the symptoms and signs of the acute type.[12]

(F). Complications.

Provided the infant survives the initial coma and shock, there is the risk, so far as the acute type of case is concerned, of progress into the chronic stage.[12] There occurs also the danger in the acute cases, especially those suffering from shock and severe dehydration, of sinus thrombosis developing owing to the increased viscosity and specific gravity of the circulating blood fluids. Both acute and chronic types are liable to develop pulmonary and upper respiratory infections,[6][15] otitis media, pyuria and skin sepsis, which if sufficiently severe will undoubtedly hasten a fatal termination. A further misfortune - excoriation of the buttocks - is also liable to develop, especially in the acute cases, and the danger of septic absorption from the raw area has to be guarded against.

(G). Pathology.

It is remarkable that the post-mortem findings in some of these infants show only slight evidence of pathological change in the various organs.[12][16] In some severe and acute cases, only a slight degree of erythema of the bowel (lower ileum) may be present, while in others with less acute onset and less marked symptoms the bowel exhibits marked inflammatory changes. This finding suggests that the degree of erythema of the bowel is no criterion of the severity of the clinical symptoms in these cases.[22] In the more severe cases, however, definite evidence of some fatty change involving most of the vital organs such as liver, kidney and heart, is present. The commonest lesion is a varying, and at times extensive, degree of fatty change in the liver tissue.[16] Quite frequently definite evidence of a terminal broncho-pneumonia or congestion of the lungs is noticed[22] - conditions which are not usually recognized on clinical examination. It may be of interest to mention here that Maizels and Smith[22] in a series of post mortems on infantile diarrhoea patients state that they frequently noted that the heart was dilated and the muscle pale - evidence of some toxic damage.

SECTION B.

A Clinical Analysis of the Case Records of 300 cases of Infantile Diarrhoea.

The following is an analysis of 300 consecutive cases of diarrhoea and vomiting admitted to the wards of Professor G.B. Fleming in the Royal Hospital for Sick Children, Glasgow, between the years of 1931 and 1934, in addition to 12 cases in whom this syndrome developed while the infants were in hospital for some other condition.

These cases may be grouped as follows:-

(a) Acute infantile diarrhoea (1) Severe type.
(2) Mild type.

(b) Chronic infantile diarrhoea.

The acute cases (severe type) are those often referred to under various names:- anhydremia[2], toxicosis[3], and cholera infantum, while the chronic cases are those known as athrepsia (Marriott). At times it may be very difficult to decide whether the cases are of the acute (mild type) or of the chronic type, but in all these cases the general condition of the infant on admission, as well as the duration of the disease, was considered before they were grouped into these various subdivisions.

In the total of 300 cases, 98 belong to the group of acute diarrhoea (severe type), two of the number dying before admission; 107 to the group of acute infantile diarrhoea with mild symptoms; and the rest, numbering 95 cases, are included under the group of chronic diarrhoea and vomiting.

TABLE I.

Type of Infantile Diarrhoea (with Mortality).

Infantile Diarrhoea	Number of Cases.	% Mortality	Total Mortality	Total Number
Acute (a) Severe type.	98	76.6%	47.2%	300 cases
(b) Mild type	107	41.1%		
Chronic type.	95	33.7%		

In the acute type with severe symptoms the mortality rate was 76.6%; for those with mild symptoms the rate was 41.1%; while in the chronic group it was 33.7%. The mortality rate for all cases in the series amounted to 47.2% (Table I).

The mortality rate in the present series of acute infantile diarrhoea does not compare very favourably with the figures given by various other investigators, except Hartmann[21], for similar infants (Table II).

TABLE II.

Mortality Figures for Various Clinics

after Cohen, Miller & Kramer[40].

Investigators	Number of Cases	% Mortality	Year.
Mourad	181	21%	1923
N.Y. Nursery & Child Hospital.	175	35%	1925-1928
Hartmann[21]	27	88%	1928
Karelitz & Schick[33]	21	14%	1931
Cohen, Miller & Kramer[40]	9	22%	1933

In the following pages all these patients are included in one group, since, although they each exhibit different stages of infantile diarrhoea and vomiting, these stages are so closely related that it would be impossible and undesirable to consider each variety under separate headings.

Of the 300 cases, only 23, a surprisingly small number, had a definite history of prematurity. These comprise 6 cases suffering from acute infantile diarrhoea and 17 with chronic diarrhoea.

TABLE III.

Incidence of Prematurity.

Type of Case	Number of Cases.	% Mortality	Total Mortality	Total Number	% of Series
Acute	6	66.6%	73.8%	23	7.66%
Chronic	17	76.0%			

The mortality rates were respectively 66.6% and 76% with a combined mortality rate of 73.8%. The finding that the mortality rate is greater in the chronic cases is possibly explained by the fact that nearly all these infants were severely undernourished and had caused much anxiety in their dietary management since birth (Table III).

Only 7 patients, 2.3% of the total, were illegitimate. This number is slightly less than the figure of 3% found by Parsons(1) as the illegitimate rate in a series of 100 patients with diarrhoea examined in Birmingham. Two of the seven were of the acute type and five of them were chronic cases. The mortality rate was respectively 100% and 60% with a total mortality rate of 71.4% (Table IV).

TABLE IV.

Incidence of Illegitimacy.

Type of Case	Number of Cases.	% Mortality	Total Morality	Total Number	% of Series
Acute	2	100%	71.4%	7	2.3%
Chronic	5	60%			

In the whole series only 2 cases, both of whom died, were found to show evidence (W.R.++) of syphilis.

The idea has long been prevalent that children admitted to hospital are very liable to develop diarrhoea and vomiting as a result, perhaps, of cross infection. Nevertheless, over a three year period only 12 patients admitted for some other condition developed diarrhoea and vomiting while in hospital and of this number 4 were patients suffering from pyloric stenosis in which the condition appeared after the performance of a successful Rammsted's operation. These patients suffering from pyloric stenosis were isolated practically from the date of their admission, so that the possibility of a cross infection occurring in them was very unlikely. It appears likely that owing to their poor general condition, the result of severe vomiting and fluid loss, the alimentary tract, inactive for so long, was unable to deal with the sudden administration of food and diarrhoea resulted. The mortality rate in these infants was 100%. In a consideration of the eight other cases developing diarrhoea and vomiting while in hospital, three were found to be suffering from severe and five from mild symptoms. The respective mortality rates were 66.6% and zero. It thus appears that many of these patients, (pylorics excluded), developing diarrhoea and vomiting while in hospital are of the mild type and usually recover with appropriate treatment (Table V).

TABLE V.

In-Patient Incidence of Infantile Diarrhoea.

Type of Case	No. of Cases	% Mortality	Total Number
(a) Severe type	3	66.6%	12
(b) Mild type	5	0%	
Operated Pyloric Stenosis.	4	100%	

The total number of cases consisted of 173 males with a mortality rate of 47.2% and 127 females with the same mortality rate. It would thus appear from this series of cases that, although the mortality rate is identical for both sexes, males appear to be more often affected than females. Sex therefore does not appear to have a significant effect on either liability

TABLE VI(a).

Sex Incidence and Mortality Rates.

Sex	No. of Cases	% of Series	% Mortality	Total Number
M.	173	57.9	47.2%	300
F.	127	42.1	47.2%	

to this condition or the mortality.

With reference to the age incidence nearly two thirds, or 65.2% of the cases occur during the first six months of life, while only 12% occur after the age of one year. Parsons[1] states that in his series most of the cases are under the age of three months, while according to Wilkins[18] it is a common saying in the United States that the child is more likely to develop diarrhoea during his second summer than during his first. He[18] demonstrated that 54% of the infants developed infantile diarrhoea during their second summers, i.e., when over one year old.

TABLE VI(b).

Age Incidence.

Age of Infants	Number of Cases	% Total	Deaths	% Mortality		Total Number
Under 1 month	19	6.3%	14	73.6%	48.8%	300 cases
1-3 months	59	19.6%	24	40.7%		
3-6 months	118	39.3%	62	52.5%		
6-12 months	68	22.6%	29	42.6%		
1-2 years	33	11.0%	12	36.3%		
Over 2 years	3	1.0%	1	33.3%		
Over 1 year	36	12.0%	13	36.0%		

It will be noticed that in the age group, under one month, the mortality rate is high, 73.6%. The cases under one year show a death rate of 48.8%, and those between one and two years, 36.3%. These figures demonstrate the seriousness of the prognosis at all ages, and the special danger in younger infants.

Findlay(12) lays stress on the seasonal incidence of infantile diarrhoea. In the year 1921, when a "real epidemic" was present, he found 64% of his cases occurring during the months of July, August and September. Nabarro(16) in 1921, from personal observations on a series of cases suffering from the same condition, found that the curve of maximum onset was the third and fourth week of July and the first week of September. In America Marriott et alii(15) discovered, on reviewing 312 cases over a three year period, that non-dysenteric diarrhoea occurred more frequently in the early autumn months, especially in those infants whose nutrition had suffered during the summer season. They(15) also noted, however, that in addition to this large group an appreciable number occurred during the winter months.

TABLE VII.

Present Series - Seasonal Incidence.

Month	Number of Cases	% of Total	% Mortality	Month	Number of Cases	% of Total	% Mortality
Jan.	8	2.6%	50%	July	33	11.0%	42.4%
Feb.	10	3.3%	60%	Aug.	47	15.6%	51.0%
March	13	4.3%	38.4%	Sept.	46	15.3%	41.3%
April	12	4.0%	66.6%	Oct.	47	15.6%	31.8%
May	19	6.3%	52.6%	Nov.	22	7.3%	63.6%
June	34	11.3%	61.7%	Dec.	9	3.0%	22.2%

From an examination of this series (Table VII), it is at once evident that the majority of the cases 68.8% occur during the summer and autumn months of June, July, August, September and October, but that except for the month of June with 61.7% mortality, the mortality figures are lower for these months than those for the winter and spring months. It was previously considered that infantile diarrhoea and vomiting was a condition pertaining to the summer months of the year but it is rather striking that in the series cases occur throughout the year, a fact which will at once dispel the idea that heat and humidity are essential for the development of infantile diarrhoea and vomiting. In other words, there is an endemic incidence with a seasonal increase from June to September.

Previous History. It is well recognised that artificial feeding plays a major rôle in the development of infantile diarrhoea, Findlay(12) stating that in a series of 320 cases examined by him, only 9% were breast-fed.

TABLE VIII.

Type of Feeding.

Type of Feeding.	Number of Cases
Artificial	290
Breast	9
Bottle & Breast	1

In this series 290 were artificially fed, 9 breast fed and one partly bottle and partly breast fed previous to admission. Only 3% of the series were breast fed, suggesting that the breast fed infants enjoy some immunity from this condition.

These cases suffering from infantile diarrhoea were admitted with a history of various abnormalities (Table IX) but by far the largest number, 237 or 79 per cent, were admitted with the complaint of diarrhoea and vomiting. Only 20, (6.6%) had vomiting alone, 13 (4.3%) had diarrhoea alone and in 30 (10.0%) the complaint was of convulsions, "not thriving" or cyanosis. In these infants, with no history of alimentary disturbances previous to admission, definite evidence of diarrhoea or vomiting or both was soon forthcoming.

In absence of any sign of disease elsewhere, and on post-mortem findings, these cases were diagnosed as gastro-enteritis and are therefore justifiably included in this series.

TABLE IX.

Complaint on Admission.

Complaint	Number of Cases.	% of Total
Diarrhoea & Vomiting	237	79%
Vomiting	20	6.6%
Diarrhoea	13	4.3%
Convulsions, Cyanosis, etc.	30	10.0%

So far as the maternal age was concerned nothing of much importance as an aetological factor could be deduced.

In a consideration of the average number of children in each household (Table X), it appears to be of some significance that the largest incidence, 35.9%, occurs in families where the mother has five or more children. This finding no doubt suggests overcrowding. The next largest incidence, 21.5%, occurs in those families where the infant happens to be the first born. This finding probably suggests that there exists some ignorance in the correct manner of feeding and caring for the child, owing to inexperience.

TABLE X.

Incidence of Infantile Diarrhoea to Size of Family.

Children in Family	Number of Cases	% of Total	Total Number
1	58	21.5%	300 cases
2	48	17.7%	
3	42	15.5%	
4	25	9.3%	
5 or more	97	35.9%	
no data	30	-	

With reference to the housing problem the details are not sufficient to give any reliable and conclusive proof that in those homes exhibiting evidence of overcrowding the liability to this condition of vomiting and diarrhoea is more marked. It is nevertheless known that this must be an important factor as the majority of cases occur amongst the poorer classes of the community in the slums of large industrial cities.

Out of the total number of 300 cases, 24 (8.1%) gave a short history of one day's duration (Table XI), while the largest number 148 (49.9%) suffered from an alimentary disturbance of over one week's duration.

Some cases of this latter group had suffered from diarrhoea continuously for seven or more days. Others had a history of intermittent gastro-enteritis, but on admission were acutely ill and were clinically indistinguishable from the acute cases. They are therefore classed as acute and not chronic cases in Table I.

TABLE XI.

Duration of Condition with Mortality.

	Duration of Condition	Number of Cases	% of Total	% Mortality	Total Number
(a)	1 day	24	8.1%	54.1%	300
(b)	1-3 days	34	11.4%	41.1%	
(c)	3-7 days	91	30.6%	45.0%	
(d)	Over 7 days	148	49.9%	53.4%	
	Not recorded	3	-	-	

Many of the cases in the former small group (a) belong to the group of cases admitted with severe toxic symptoms and it is not at all surprising that the mortality rate is high, 54.1%.

The mortality rate per group (d) is also high, 53.4%, due no doubt to the fact that the resistance of many of these infants has been lowered by long continued intestinal disturbances and atrophy, as well as the frequent occurrence in many of them of an acute exacerbation of their symptoms.

<u>Symptomatology.</u> It has been previously mentioned in this paper, that 96 patients on admission showed signs of severe dehydration, cyanosis, or were acutely ill and two died before admission to the wards (Table I). These patients were grouped under acute infantile diarrhoea (severe type). Included in this group were 38 cases suffering from acute and severe dehydration, 22 who were cyanosed and acutely ill, and 36 who exhibited severe toxic symptoms and were badly dehydrated. The mortality rate for each sub group was high (viz.) 71.3%, 85.0% and 73.5% respectively (Table XII).

<u>TABLE XII.</u>

<u>Condition of Patients on Admission.</u>

Type of Case	Clinical Condition	Number of Cases	% of Total	% Mortality
Acute (Severe)	Severe dehydration.	38	12.0%	71.3%
	Cyanosed & acutely ill.	22	6.8%	85.0%
	Toxic and dehydrated.	36	11.4%	73.5%
Acute (Mild)	Slight dehydration.	67	22.8%	37.3%
	Moderate dehydration.	40	13.7%	47.5%

TABLE XII (Contd.)

Type of Case	Clinical Condition	Number of Cases	% of Total	% Mortality
Chronic	Ill but no dehydration.	48	15.8%	48.0%
	Not acutely ill, no dehydration.	47	15.7%	19.1%
Acute	Died before admission.	2	0.7%	-

Amongst the 107 patients, considered to be suffering from acute infantile diarrhoea but of mild severity, 40 were ill and showed evidence of moderate dehydration, while 67 showed evidence of only slight dehydration. The mortality rate of these sub-groups was 47.5 and 37.3% respectively (Table XII). On examining the cases which comprise the chronic group, 48 were found to be ill but showed little evidence of clinical dehydration while 47, although wasted, were neither ill nor did they show any evidence of dehydration. The mortality rate was 48% in the former sub-group and 19.1% in the latter. It thus becomes quite evident from these figures that the more acute the signs and symptoms on admission, the worse the prognosis and the higher the mortality rate.

From an examination of the Table XIII, it is apparent that more than two thirds of the cases in this series had varying degrees of fever on admission. Forty cases (13.3%) exhibited readings of over 102°F, while at the other extreme was a small group of 16 cases showing definitely subnormal readings. Many of the patients in the latter group were very acute toxic cases and showed all the signs of severe collapse.

TABLE XIII.

Admission Temperature (Rectal).

Temperature	Number of Cases.	% of Total	Total Number.
Subnormal	16	5.3%	
98°-99°F.	30	10%	
99°-100°F.	112	37.3%	300
100-102°F.	100	33.3%	
Over 102°F.	40	13.3%	
Not recorded	2	0.66%	

It has been suggested by Finkelstein[8] that the presence of fever in these cases is due partly to a high carbohydrate diet and partly to a negative water balance. Marriott[14], on the other hand, although he credits a negative water balance as the cause of this fever, lays much greater stress on parenteral infection which he maintains is so often met with in these cases. Schoenthal and Morton [41] are definitely in favour of the view that the fever in many cases results from water depletion, for they were able to demonstrate that by limiting the water intake of a five and a half month infant, as well as changing its diet to a small volume, high caloric one, the infant developed fever.

On examination of the alimentary symptoms while in hospital, 189 cases had at one time or another both vomiting and frequent loose stools, 68 had "mild" stools but no attacks of vomiting, while 19 had bad foul smelling, watery and frequent stools but no vomiting. In only 5 cases was there no evidence of loose stools or vomiting and only 4 had attacks of vomiting when the stools were normal. All these cases were admitted with a history of wasting, diarrhoea and vomiting, and of the seven cases terminating fatally, the post-mortem findings were consistent with the diagnosis of infantile diarrhoea and vomiting (Table XIV).

TABLE XIV.

Alimentary Symptoms and Mortality Rate.

Alimentary Symptoms	Number of Cases	Number of Deaths	% Mortality	% of Total	Total Number
Nil	5	4	80%	1.66%	300
Vomiting only	4	3	75%	1.33%	
Vomiting & Diarrhoea	189	96	50.8%	63%	
"Bad" Stools only	22	13	49.1%	7.3%	
"Mild" Stools only	68	16	23.5%	22.6%	
Not classified	12	-	-	4.0%	

From these figures it would appear that there is an important significance about the actual observation of the patient.

A reasonably good prognosis accompanies a mild diarrhoea, the succeeding stages in severity being, severe diarrhoea, diarrhoea and vomiting, and the most grave where, in spite of the history and obvious acute illness, there is neither diarrhoea nor vomiting.

In a consideration of the parenteral infections encountered in this series of patients, 122 cases (40%) were found to be suffering on admission or during their sojourn in hospital from such varied conditions as otitis media, pyuria, bronchitis, throat infections and broncho pneuomonia. In previous pages the importance of parenteral infections as stressed by Karelitz[6], Marriott et alii[12][15], in the production of diarrhoea and vomiting in infants has been discussed. The former two authors demonstrated that 50% and 83% respectively of their series suffered from some parenteral infection.

The largest individual group in this series were 78 cases suffering from otitis media. In a consideration of the mortality rate for the various parenteral infections, those with broncho pneumonia, 9 cases, appear to head the list with a mortality rate of 88%. followed by cases of pyuria 73.6%. In taking into consideration the age groups for the various parenteral infections it is quite evident that the younger the infant the higher the mortality rate (Table XV).

TABLE XV.

Incidence of Parenteral Infections.

Parenteral Infection	No. of Cases	% Mortality	% of Total	Age Factor	No. of Cases	% Mortality	Total Number
Otitis Media.	78	42.3%	26%	0-6 month	49	47%	
				6-12 "	19	42%	
				Over 1 yr.	10	20%	
Broncho Pneumonia	9	88%	3%	0-6 month	5	100%	
				6-12 "	2	100%	
				Over 1 yr.	2	50%	
Pyuria	11	73.6%	3.66%	0-6 month	4	100%	
				6-12 "	5	60%	
				Over 1 yr.	2	50%	
Furunculosis.	5	60%	1.66%	0-6 month	5	60%	
				6-12 "	-	-	122 cases
				Over 1 yr.	-	-	
Umbilical Sepsis.	3	66.6%	1.0%	0-6 month	3	66.6%	40.6%
				6-12 "	-	-	
				Over 1 yr.	-	-	
Bronchitis	4	50%	1.33%	0-6 month	3	66.6%	
				6-12 "	1	0%	
				Over 1 yr.	-	-	
Combination of above.	11	72.7%	3.66%	0-6 month	7	71.3%	
				6-12 "	4	75%	
				Over 1 yr.	-	-	
Throat Infection	1	-	0.33%	6-12 month	1	0%	

It appears of some importance to emphasize the fact that many of these patients showed no evidence of parenteral infection on admission, but appeared to develop it after the onset of the alimentary symptoms. There is also the possibility that some parenteral infections in this series were missed on clinical examination, so that the incidence may be higher than 40%. An examination of the post mortem material however will definitely elucidate this point. These results thus indicate that in this series of patients suffering from diarrhoea and vomiting, the incidence of parenteral infections is not as high as in similar series investigated by various authors, (6), (12),(15),(22).

Percentage Expected Weight on Admission. With reference to the percentage of expected weight, only 103 cases, (37.2%), were 80% or over, while as many as 172, (62.8%) showed values under this figure (Table XVI). These findings suggest that many of the patients were suffering from various degrees of chronic "atrophy" even although many of them were, when first seen, definitely suffering from the symptoms of an acute intestinal derangement.

Confirmation is therefore available of the belief that undernourished, and presumably ill-cared-for, children are specially liable to develop gastro-intestinal disorders.

TABLE XVI.

Percentage Expected Weight on Admission.

% Expected Weight	Number of Cases.	% of Total	% Mortality	Total Number
100% or over	17		23.3%	
90-99%	30	37.2%	40.0%	
80-89%	56		35.7%	
70.79%	78		35.8%	300 cases
60-69%	53		53.0%	
50-59%	27	62.8%	77.7%	
40-49%	11		81.8%	
Under 40%	3		100%	
Not tabulated	26		-	

When the mortality rate for each sub-group is considered it is quite evident that those nearer the normal percentage expected weight i.e., 100%, show a lower figure than those badly undernourished. It might also tentatively be suggested that the high mortality rate of 47.3%, (Table I), in the series of 300 patients may be explained by the fact that such a large percentage of cases (62.8%) exhibit marked evidence of atrophy and wasting.

Duration of Hospitalisation. From the data compiled (Table XVII) it will be noticed that the largest number of deaths (70) occurred during the first week in hospital, while if the second week be included, the number rises to 100.

TABLE XVII.

Hospital Sojourn. Deaths & Recovery Cases.

Time in Hospital	Discharged Well	Deaths	Mortality Rate	Total Number	
1 week or under	19	70	78%	89	300 cases
2 weeks	58	30	34%	88	
3 weeks	29	19	39%	48	
4 weeks	19	14	42%	33	
Over 4 weeks	33	9	21%	42	

A small number (19) responded to treatment during the first week and were discharged, but of this number most were of a rather mild type. The largest number of cases that recovered did so either during the second week or after four weeks, suggesting that, provided the infant can be kept alive for at least two weeks, the ultimate prognosis is very materially improved.

Re-Admissions. In the whole series only 8 cases were re-admitted at some later date with a history of alimentary derangement similar to their previous complaint. Of this number three terminated fatally, while the rest were discharged home well.

Pathology. For the reports of the post-mortem examination I am indebted to Dr J. W. S. Blacklock, Pathologist to the Royal Hospital for Sick Children.

In all, the post-mortem findings of 91 cases are set down for consideration. Included in these are 4 cases of pyloric stenosis in which diarrhoea and vomiting developed after operation. The only parenteral infections discovered at post-mortem, not previously recognised clinically, were several cases with a terminal broncho pneumonia and a few cases of mild otitis media. These reports (Table XVIII) indicate that a total number of 47 cases were found to be suffering from infantile diarrhoea without any evidence of parenteral infections. In this group are 4 cases of pyloric stenosis developing diarrhoea and vomiting after operation, and three cases with superior longitudinal sinus thrombosis. Twenty cases were found to be suffering from infantile diarrhoea and an associated broncho pneumonia, the latter condition in 9 cases being terminal. The remainder, 24 cases, exhibited evidence of otitis media, broncho pneumonia with otitis media or pyuria in association with the gastro enteritis. In these 44 cases with definite post-mortem evidence of parenteral infection it was impossible, except in 9 with terminal pneumonia, to state whether this condition had occurred prior to the development of the alimentary symptoms or whether it was of later onset.

TABLE XVIII.

Parenteral Infections Discovered at Post-Mortem.

Post-Mortem Diagnosis	Number of cases	% of P.M.	Total
Gastro-enteritis	40	44.0%	
Operated Pyloric Stenosis	4	3.8%	51.3%
Sinus Thrombosis + G.E.	3	3.5%	

TABLE XVIII (Contd.)

Post-Mortem Diagnosis	Number of cases	% of P.M.	Total
B. Pneumonia + G.E.	*20	22.0%	
Otitis Media + G.E.	9	10%	48.7%
B. Pneumonia + O. Media + G.E.	12	13%	
Pyuria + Gastro-enteritis.	3	3.5%	

*9 cases of Broncho Pneumonia exhibited only a Terminal Pneumonia.

G.E. indicates gastro-enteritis.

The post-mortem findings in most of these infants indicated various degrees of inflammatory change in the small bowel, the severity however bearing no definite relationship to the acuteness of the symptoms. There were also fatty changes in most of the organs, especially marked and characteristic in the liver tissue.

These findings, in conjunction with those in Table XV, indicate that so far as this series of cases is concerned the presence of parenteral infection is not so common as figures published by Karelitz[6], Marriott et alii[15][22] for similar cases suffering from the alimentary disturbances of infancy suggest.

Conclusions.

From the analysis of 300 case records it seems that:-

(1) The children most prone to infantile diarrhoea are either the first born or the younger members of large families. Of the present series 21% were "only children" and 36% came from families of five or more. This suggests two causative factors - (a) inexperience in infant hygiene and (b) overcrowding or inability of the mother to devote sufficient attention to the individual members of the family.

(2) Among the predisposing circumstances are artificial feeding, age and the state of nutrition. Of the 300 cases, 291 were artificially fed and only 9 were on the breast. Younger infants suffered more frequently, 65% occurring in the first six months of life. The majority of the series was badly nourished. Approximately two thirds of the total being less than 80% of expected weight.

(3) The sex factor is not of great importance, though more males were affected (58%) than females (42%).

(4) Infantile diarrhoea is endemic, but subject to a seasonal increase between June and October.

(5) Very few cases develop de novo in hospital, only 12 occurring in the period covered by this investigation.

(6) Given a history of diarrhoea and vomiting, the only clinical features of significance are a toxic appearance and the presence of dehydration.

(7) 40% of the series had some parenteral infection noted on clinical examination. The figure for cases that came to post-mortem was 48%, confirming the suspicion that parenteral infection may not be so common as other workers have stated.

(8) The pathological findings were varying degrees of erythema of the mucous membrane of the small intestine and fatty change in many organs, particularly in the liver. The degree of inflammation of the bowel bore no relationship to the severity of the clinical symptoms.

(9) The mortality rate of the series was 47.2%.

(10) Many factors influence the mortality - prematurity, illegitimacy, age of patient, malnutrition, the severity and duration of the disease. Half of the fatalities occurred during the first week of hospitalisation, whilst 80% of patients who survived 4 weeks in hospital recovered. This suggests the necessity for earlier and more energetic treatment.

PART II.

SECTION A - The Blood Chemistry in Infantile Diarrhoea.

SECTION B - Variations in the Composition of Blood as a Result of Parenteral Administration of Saline and Glucose.

PART II. SECTION A.

BLOOD CHEMISTRY IN INFANTILE DIARRHOEA.

Introduction.

At one time it was considered that the blood did not change its concentration but that under different conditions it tended to keep its composition constant and that, when necessary, fluid from different water depots could be drawn upon to supply any defect. We now know, however, that alterations of the blood and its constituents do take place in conditions of dehydration and acidosis (14) although there does remain a tendency, the mechanism of which is unknown, for the concentration to remain within certain narrow limits.

The presence of blood concentration in diarrhoeal cases has been described at various times, and by different observers, using the R.B.C. and Hb content, dye methods, water content of dried weight of unit volume of blood, the serum proteins and haematocrit readings. Maizels and Smith (22) et alii mention that variation of fluid content of the blood can be demonstrated by Hb estimation. Marriott (11) describes an increased proportion of total solids, increase in the R.B.C. count and Hb value, and concentration of serum proteins in cases with acute and severe dehydration.

It is known however that the estimation of R.B.C. and Hb - Lee and Mulder (42) - is liable to too many variations to be a satisfactory index of blood volume and blood concentration. Similarly blood volume estimations by use of vital red and other dyes are open to large margins of error, especially in acutely ill patients suffering from infantile diarrhoea in which, as we know, there occurs stasis or partial stasis of the circulatory volume in the subcutaneous capillaries of the body. The accuracy of the dye method in estimating the circulating blood volume has also been questioned by Miller and Pointdexter [43] in their experimental work on dogs.

According to Lee and Mulder [42] et alii, [36], [52] the serum protein value is the least objectionable index of blood concentration though here again the possibility of protein being passed into or out of the circulation cannot be definitely excluded. At present the haematocrit value appears to be the most reliable index of blood volume change but unfortunately in a study on infants, especially when several specimens are required within a short interval of time, the practicability of the method is strictly limited. Consequently, the serum protein has been employed as the indicator of blood concentration in the present investigation.

Mention has been made in a previous chapter of the effect of dehydration and water loss on the infant as a whole. The object of this chapter of the paper is to report (A) the blood chemistry in infantile diarrhoea and (B) the variations in the composition of the blood as the result of parenteral administration of saline and glucose.

<u>Saline Administration - Technique</u>.

In most cases fluid was given intra-venously, into the superior longitudinal sinus - a method simple and easy in young infants, and in no way dangerous in experienced hands. From 20-25 ccs. of fluid per kilogram of body weight were usually given, care being taken that the fluid was run in at a slow and regular rate to prevent any embarrassment of the circulation.

In all cases the blood samples were removed and infusions administered shortly after the admission of the infants to hospital, and although Howe[43a] has shown that very little alteration in the serum proteins occurs as the result of giving or withholding food, nothing was given by mouth for a period of three hours after the infusion. The same procedure was adopted for normal and control infants.

In most cases combined isotonic saline and 10% glucose solution was used for the infusions but in several cases the effect on the serum proteins of isotonic saline alone was examined. The difficulties attached to removal of specimens of blood from dehydrated patients are obvious. Accordingly only small specimens, taken from the heel, just sufficient for an examination of the serum proteins, were removed from many, while in others, whose symptoms were not so acute, blood was obtained from the scalp or other superficial vein in sufficient amount to permit the determination of chloride, non-protein nitrogen and sugar by micro-methods.

Methods.

In those patients, where the serum protein only was examined, a very small quantity of blood (0.5 c.c.) was removed by pricking the infant's heel. The blood was permitted to clot, and the estimation made by use of the Zeiss dipping refractometer.

Where larger samples were available, blood was collected under paraffin and the haemotocrit values read after spinning in the centrifuge for 30 minutes.

Blood and plasma chloride values were estimated by Van Slyke's[44] method. The N.P.N. was estimated by the micro Kjeldahl combustion[45] method and the blood sugar by the method of Folin-Wu[46].

At the commencement of these investigations, attempts were made to estimate the water content of the blood by the use of previously weighed filter paper, which then had blood placed on it. The papers were immediately re-weighed, dried in an oven kept at a constant temperature, and weighed a third time. In this manner the water content of the blood could be calculated. Inaccuracies however were noted in the method, owing to rapid evaporation during the re-weighing, and it was abandoned.

(A). The Serum Proteins.

(a) Normal Infants. According to Nast[47] there are five periods in infancy for protein concentration of the blood serum:- (1) one to three months, (2) three to eight months,

(3) eight to eighteen months, (4) one and a half years to five years and (5) five years to fourteen years. With the increase in age the values steadily rise until the value in the last two stages is similar to the value found in adults. Employing the refractive index Mello-Leitao[48] confirmed these findings for the different age periods as follows -

(1) 1-3 months	-	5.19-6.29	gms.	%
(2) 3-8 months	-	6.0-6.87	"	"
(3) 8-18 months	-	6.47-7.28	"	"
(4) and (5)	-	8.05 gms. %		

and thus demonstrated that the serum protein values for young children are very much lower than the values in the case of adults. Darrow and Cary[49] also substantiate these findings but criticize the employment of the refractive index in their determination. Webb[50] however demonstrates values for infants, aged one to six months, varying between 5.46 and 6.90 gms. % with an average of 6.04 gms. % and also states that some of the cases in his series were from 13 to 40% under weight but that, when infection is excluded, no significant change in the serum protein values occurs. Rennie[51] however, using the micro-Kjeldahl method, did not find much difference in the values for total serum protein between infants and older children.

It should be noted that most of the serum protein values for infants, published in the literature, have been estimated by means of the refractive index. Darrow and Cary[49] et alii[51] state that the results thus obtained are not to be relied upon as the presence of excessive lipoid in the serum will result in too high a reading being obtained. Cohen et alii[40], however, in their group of infantile diarrhoea cases, found rather close agreement between the refractometric and the Kjeldahl methods in the estimation of serum proteins.

In cases where the exact serum protein is not necessary, but where it serves as a standard for the measurement of blood hydration, the values as given by the refractive index are sufficiently accurate. It is also the method of choice in patients with severe dehydration when several specimens of blood are to be removed within a short space of time.

The total serum proteins for a group of eight infants under the age of one year are set down in Table XIX. Many of these patients suffered from tetany or other manifestations of the nervous system but none of them were considered to be acutely ill. They showed neither evidence of fever nor signs of dehydration.

TABLE XIX.

Serum Proteins : Normal Infants.

Name	Age (Months)	Disease	Total Serum Protein gms. %
J.C.	5	Tetany	(6.25-6.45) Average 6.33
J.G.	5	Hydrocephalus	6.92
J.M.	6	Hydrocephalus	7.51
J.N.	6	Tuberous Sclerosis	(6.01-7.15) Average 6.55
C.S.	6½	Tetany	7.35
J.McK.	7	Tetany	7.28
T.McG.	12	Rickets	7.33
C.S.	12	Syphilis	(7.06-7.74) Average 7.38

The serum protein values varied between 6.01 gms. % and 7.74 gms. % and no relationship between the age and the serum protein values as described by East et alii[(47),(48)] was evident from an examination of this small series.

(b) Acute Infantile Diarrhoea. Marriott[(14)] has demonstrated that the serum proteins, in infants with severe and acute diarrhoea, are usually raised well above the values for similar normal infants. These findings have been confirmed by a large number of other observers,[(50),(53)] but Cohen et alii[(40)] in a series of theirs found that only four out of nine cases of acute infantile diarrhoea had serum protein values of 8 gms. % or over.

The patients in the present series were all suffering from acute infantile diarrhoea. The values for serum protein were obtained on admission or shortly after admission, but previous to the administration of any intra-peritoneal or intravenous saline or glucose infusions. Eleven of them (Table XX) exhibit rather high values for serum proteins, varying between 8.46 gms. % and 10.19 gms. %, while five show readings between 6.96 gms. % and 7.85 gms. %.

Two (marked with asterisk) of the patients in this latter group had been ill for some time and may have been cases of chronic diarrhoea, but on admission they were acutely ill and have therefore been grouped with the other acute cases.

TABLE XX.

Serum Proteins : Acute Infantile Diarrhoea.

Name	Age (weeks)	Serum Protein gms. %	Remarks
R.W.*	8	7.37	Severe Dehydration -o-
H.C.	8	7.28	Cyanosed, Dehydrated
D.L.	12	8.62	Severe Dehydration -o-
R.M.*	15	7.65	Toxic, " -o-
M.B.	16	8.46	Toxic, " -o-
J.M.	19	9.21	Severe Dehydration -o-
J.S.M.	19	6.96	Moribund, Dehydrated
R.G.	20	9.91	Severe Dehydration -o-
V.F.	22	7.85	" " -o-
A.S.	24	10.03	Cyanosed, Dehydrated
J.O'H.	30	8.48	Toxic Dehydration
H.McN.	32	9.39	Severe " -o-
J.S.	40	9.48	" " -o-
B.I.	47	8.82	" " -o-
I.M.	$1\frac{3}{12}$ Yrs.	10.19	" "
A.J.	$1\frac{5}{12}$ Yrs.	8.91	" " -o-

-o- = fever.

Many of these patients had varying degrees of fever but this can probably be discounted, as Webb[50] maintains that fever has only a slight and transitory effect on the total serum proteins.

(c) <u>Chronic Infantile Diarrhoea.</u> In a series of marasmic infants mostly under the age of one year Courtney and Fales[54] discovered that blood solids were slightly below the normal average. Marriott[11] has also pointed out the fact that in athreptic infants there occurs a reduction of the serum proteins as well as diminution of the Red Blood Corpuscles and the Hb value. This, he suggests, is due to either hydraemia - the result of tissue break-down - or to destruction of protein and haemoglobin. Wiley and Wiley [55] are of the opinion however that, while blood may be the first to give up water during dehydration, the ultimate effect is a restoration of the blood volume at the expense of the cellular water. This might possibly explain the alterations in serum protein and Hb values found in chronic diarrhoea. Marriott[14], however, has also demonstrated that while the blood volume in normal infants was 9.1% of the body weight, in athreptic infants it amounted to only 8% of the body weight. This finding rather suggests that hydraemia does not occur in these infants and that the decrease in protein and Hb is possibly due to their destruction. The low serum protein values in these cases with chronic infantile diarrhoea have been confirmed by the studies of Utheim[36] and Webb[50].

It may also be of interest to note that, according to Underhill and Fisk[56], animals suffering from large fluid losses as a result of pilocarpine injections, the serum proteins ultimately show a fall, if the injections are continued for a sufficiently long period of time.

TABLE XXI.

Serum Proteins : Chronic Infantile Diarrhoea.

Name	Age (weeks)	Serum Protein gms. %	Remarks.
B.P.	2	5.72	D. & V., Marasmus
W.McF.	3	7.53	D. & V., Not Thriving
C.D.	8	4.92	D. & V., Marasmus, Pyuria
M.M.	8	6.18	D. & V., Marasmus
P.H.	8	6.09	D. & V., "
A.H.	11	6.49	D. & V., "
F.C.	12	7.04	D. & V., "
A.M.	15	6.70	D. & V., " , Pyuria
J.McP.	15	7.04	D. & V., "
W.McD.	6½	6.03	D. & V., "
M.McI.	30	6.68	D. & V., "
M.C.	30	6.31	D. & V., Dehydration slight.
A.McL.	38	6.85	D. & V., Broncho Pneumonia later.
C.B.	40	8.51	D. & V., 2 weeks.
W.A.	45	7.78	D. & V., Marasmus

D. & V. = Diarrhoea and vomiting.

The serum protein values are set down In Table XXI for 15 cases of chronic infantile diarrhoea. They show rather variable readings, only two with values of 7.78 gms. % and 8.51 gms. % being on the high side, the remainder being lower or nearer the values for normal infants given previously (Table XIX).

These findings confirm in a way those of Marriott[14] et alii[36][50] in that, in the acute cases, the serum protein values are usually high while, in the chronic ones, the values are usually lower than the values found for normal infants.

(B). <u>The Blood and Plasma Chlorides</u>.

(a) <u>Normal Infants</u>. In an examination of the blood and plasma chloride values of normal infants it will be noted (Table XXII) that the blood chloride value varies between 81.4 c.c. and 88.5 c.c. $\frac{N}{10}$ Cl while the plasma chloride varies between 103.6 c.c. and 108.5 c.c. $\frac{N}{10}$ Cl. These readings appear to be within normal limits[54].

TABLE XXII.

Various Blood Constituents. Normal Infants.

Name	Age (mths.)	Disease	N.P.N. mgs. %	Blood Chloride ccs. N/10 Cl.	Plasma Chloride ccs. N/10 Cl.	Sugar mgs.%
J.G.	5	Hydrocephalus	25.5-30.7	-	-	74.2
J.M.	6	Hydrocephalus	35.5-38.2	-	-	94.0
J.N.	6	Tuberous sclerosis	21.5	81.4	108.5	-
C.S.	6½	Tetany	19.1	85.3	103.6	-
J.McK.	7	Tetany	40.0	88.5	-	-
C.S.	12	Syphilis	25.0	86.3	105.9	-

(b) Acute Infantile Diarrhoea. Hartmann[21] has demonstrated that the typical serum electrolyte picture of infants suffering from acute and severe diarrhoea, is reduction of total base, with bicarbonate deficit, the chloride being normal or increased. Hoag and Marples[57] have also demonstrated variations in the blood chloride of a series of acute infantile diarrhoea cases examined by them, 10 being above the average chloride value and 15 below it. Similar observations have been reported by Maizels and McArthur et alii[58][54][59].

TABLE XXIII.

Various Blood Constituents. Acute Diarrhoea.

Name	Age (weeks)	N.P.N. mgs.%	Chloride* ccs. $\frac{N}{10}$ Cl.	Sugar mgs.%
R.W.	8	54.9	-	-
H.C.	8	21.7	69.6	
D.L.	12	52.6	-	-
R.M.	15	47.1	-	91.3
M.B.	16	90.9	74.96	-
J.M.	19	96.1	-	-
J.S.M.	19	42.7	111.5 (P)	-
D.T.	15	40.3	96.1	-
R.G.	20	-	68.0	-
V.F.	22	37.3	-	-
A.S.	24	73.5	83.6	-
J.O'H.	30	66.6	92.8	-
H.McN.	32	97.4	84.7	-
B.I.	47	55.5	79.44	-
I.M.	$1\frac{3}{12}$ yrs.	-	85.4	-
A.J.	$1\frac{5}{12}$ yrs.	67.5	-	123.8

*P - plasma chloride : other figures - blood chloride.

In an examination of the blood chloride values in this series of acute infantile diarrhoea's (Table XXIII), three show values rather on the low side, viz., 68.0 c.c., 69.6 c.c. and 74.9 c.c. $\frac{N}{10}$ Cl; four values are within normal limits, viz., 79.4 c.c. to 85.4 c.c. $\frac{N}{10}$ Cl; while two cases show definitely high blood chloride 92.88 c.c. and 96.1 c.c. $\frac{N}{10}$ Cl. In only one patient (J.S.M.) was the plasma chloride value estimated and in this case it appeared to be definitely high. These findings are thus in agreement with those of other investigators that, in acute diarrhoea, the blood chlorides are sometimes high, sometimes low and sometimes normal.

(c) Chronic Infantile Diarrhoea. Courtney and Fales[54] have demonstrated that, in athreptic infants, the blood chloride values are often low but sometimes normal or high.

In the present series of chronic infantile diarrhoea's (Table XXIV) it will be observed that the blood chloride value varies between 59.4 c.c. and 80.25 c.c. $\frac{N}{10}$ Cl, while the plasma chloride value of one patient (C.B.) was 90.0 c.c. $\frac{N}{10}$ Cl. These values for both the blood and plasma chloride are rather low and may be due to the long continued malnutrition and loss of chloride by the bowel and vomitus.

TABLE XXIV.

Various Blood Constituents. Chronic Diarrhoea.

Name	Age (weeks)	N.P.N. mgs.%	Chloride* ccs. $\frac{N}{10}$ Cl.	Blood Sugar mgs.%
B.P.	2	50.0	-	-
W.McF.	3	-	59.36	-
C.D.	8	27.7	-	-
M.M.	8	11.3	78.8	-
P.H.	8	36.8	-	-
A.H.	11	56.9	-	55.6
F.C.	12	52.6	71.5	-
A.M.	15	51.0	-	-
J.McP.	15	34.2	70.35	-
M.McI.	30	20.8	-	-
M.C.	30	17.9	70.45	-
A.McL.	38	31.2	80.25	-
C.B.	40	22.9	70.3 90.0 (P)	-
W.A.	45	41.3	-	-

*These are blood chlorides except P which is plasma chloride.

(C). Non-Protein Nitrogen.

(a) Normal Infants. The non-protein nitrogen in infants appears to be very similar to the value in adults. It may generally be accepted that a value below 40 mgs. % is normal. All the figures tabulated for this series of normal infants fall within this limit (Table XXII).

(b) Acute Infantile Diarrhoea. A great deal of discussion and interest has centred round the non-protein nitrogen and urea values of the blood in cases suffering from severe infantile diarrhoea. The general impression is that the N.P.N. levels are frequently higher than normal in these patients with severe and acute symptoms.

It was demonstrated by Schloss[38] that in infantile diarrhoea there occurred a decrease in the phenolsulphonphthalein output by the kidney and an increase in the total blood nitrogen. Similarly Schoenthal, Lurie and Kelly[39] showed that there is a diminished urea clearance in these infants and an increase in the blood urea. Cohen, Miller and Kramer[40] suggested a close relationship between the N.P.N. and the toxicity of the cases, since in four of their most toxic patients the values varied between 120 and 140 mgs. %. The presence of this increased non-protein nitrogen or urea has been confirmed by the work of Marriott[14], Nobecourt[60] et alii[21]. In contrast to these findings, Hoag and Marples[57], in a series of acute infantile diarrhoea patients examined by them, found that no increase in the non-protein nitrogen occurred except in a moribund infant.

On examination of the non-protein nitrogen readings in this series of acute infantile diarrhoeas (Table XXIII), the values appear high in some cases and normal in others. In ten patients the values vary between 47.1 and 97.4 mgs.%; three values are in the neighbourhood of high normal, viz., 37.3, 40.3 and 42.7 mgs. %; only one is definitely within normal limits - 21.7 mgs.%. These results suggest that in most patients suffering from acute infantile diarrhoea, there is an increase in the blood non-protein nitrogen.

According to Schloss[38] this increase of the non-protein nitrogen is not sufficiently explained by the increase of blood concentration, but is more likely due to a diminished kidney function - the result of depleted water supply. Marriott[11] however suggests that the cause is not only a deficient kidney action but also accelerated destruction of tissue protein. It might be of interest to note that Hartmann[61], struck by the low total electrolyte found in these cases, suggested that the increase of N.P.N. was an attempt on the part of the body to raise the osmotic pressure to its normal level. Mach[62] et alii[63],[64] have also suggested that the raised N.P.N. present in pyloric stenosis was due not so much to renal insufficiency as to a low blood chloride, which is one of the characteristic findings in the blood of this type of patient.

This relationship between the blood chloride and the N.P.N. has been vigorously denied by Kerpel-Fronius[65]. Schoenthal and Morton[41] have however produced experimental evidence in the case of a normal infant that renal insufficiency, due to a negative water balance, was the main factor in the raising of the N.P.N..

(c) Chronic Infantile Diarrhoea. In cases suffering from chronic diarrhoea and vomiting Nobecourt[60] demonstrated an increase in the spinal fluid urea. These findings have not been confirmed by Rhomer, Welsdorf and Dreyfus[66] who found a normal spinal fluid urea in all cases suffering from athrepsia with diarrhoea.

Examination of the results in these patients suffering from chronic infantile diarrhoea shows that the non-protein nitrogen values of all but four are within normal limits. In these four infants, the values varied between 50.0 and 56 mgs.% (Table XXIV).

These findings suggest that, although a lowering of the non-protein nitrogen is usually present, certain cases do show an increased N.P.N. value due possibly to severe tissue protein breakdown and a negative water balance.

(D). Blood Sugar Content.

Very few references have been made by the above-mentioned investigators, to the blood sugar values in patients suffering from infantile diarrhoea, except Marples et alii[67] who found that the fasting blood sugar values were somewhat higher in several dehydrated infants, than in a similar group of normal infants.

Very few estimations on the blood sugar value have been carried out in this series, but all that have been estimated, in both acute and chronic infantile diarrhoea, appear to be within normal limits.

(E). <u>R.B.C. and Plasma Volume % (Haematocrit)</u>.

Darrow and Buckmann[52] have demonstrated that a diminution of plasma volume occurred in patients with dehydration. Schiff[68] regards the dehydration of the plasma as running closely parallel to that of the subcutaneous tissues - fluid loss affecting the one as much as the other. On the other hand, Gamble[69] maintains that the blood only acts as a vehicle for the transport of water from the sources of supply, such as the interstitial reservoirs and the site of demand - in diarrhoea the intestinal lumen. McIntosh et alii[53] are in agreement with the views of the latter author as they discovered no relationship between the reduction of plasma volume and the severity of the dehydration, in a series of dehydrated infants.

According to Soule et alii[70] the normal percentage volume of red cells (haematocrit), varies between 19.0 and 45.0 (average 29.8) in infants under one year. In two normal infants of this series (Table XXV, cases J.N. and C.S.) the values varied between 30.8 and 36.4, while in infants suffering from acute diarrhoea the values varied between 29.6 and 44.0. In the case of R.G. the R.B.C. percentage volume amounted to 44.0

TABLE XXV.

R.B.C. and Plasma Volume % (Haematocrit).

Name	Age. (weeks)	Type of Case	Serum Protein gms.%	Haematocrit R.B.C.%	Plasma %
J.N.	25	Normal	6.55	36.4	63.6
C.S.	27	"	7.35	30.8	69.2
D.T.	15	Acute	-	39.6	60.4
R.G.	20	"	9.91	44.0	56.0
V.F.	22	"	7.85	32.4	67.6
A.S.	24	"	10.03	29.6	70.4
M.M.	8	Chronic	6.18	25.0	75.0
J.McP.	15	"	7.04	36.9	63.1
A.McL.	38	"	6.85	42.5	57.5

and it will be noted that the serum protein was also high (9.91 gms. %). The association of a high serum protein with diminution in the percentage volume of the plasma suggests that water had been withdrawn from the latter fluid and that a true anhydraemia was present. In A.S. where the percentage volume of red cells was 29.6, the serum protein was remarkably high (10.03 gms. %). Possibly the reduction of the percentage volume of R.B.C. in this case was due to the presence of anaemia, for the high serum protein reading does not indicate the presence of hydraemia. In the patients with chronic diarrhoea the serum protein values were low, while alterations of the R.B.C. volume % were not significant, varying between 25 and 42.5%.

It thus appears that in some of the cases of acute infantile diarrhoea with dehydration, anhydraemia of the plasma does occur, while in others no definite evidence of this is forthcoming from these results. In the latter cases, however, it is possible that a reduction in the total red cells (anaemia) might mask a withdrawal of water from the plasma as in case A.S.. It is therefore essential to know the total circulating plasma volume in addition to the percentage volume before deciding whether or not anhydraemia is present. Unfortunately in the present series, the infants were too ill to permit of such a determination.

Conclusions.

The blood findings in these cases with acute infantile diarrhoea may thus be accepted as an increase of serum proteins, a high non-protein nitrogen, variable blood chlorides and indefinite variations in the R.B.C. and plasma volume % (haematocrit), while the blood sugar remains within normal limits.

In chronic patients the serum proteins are usually lowered, the non-protein nitrogen values variable, the blood chloride usually slightly lowered while the sugar remains within normal limits but slightly on the low side.

SECTION B.

Variations in the Composition of Blood as a Result of Parenteral Administration of Saline and Glucose.

It has been demonstrated by many [(40), (57), (67)] that as the result of fluid administration to infants suffering from diarrhoea and vomiting there results an improvement in their general condition; the kidneys commence to secrete urine, the acidosis disappears, and the dehydration becomes less marked. Nevertheless the action of this fluid on the circulation and tissues is imperfectly understood.

(A). Repeated Saline and Glucose Injections - Acute Infantile Diarrhoea.

In Table XXVI the effect and results of repeated infusions of intra-venous or intra-peritoneal saline and glucose solutions extending over a period of days or weeks are shown in so far as they affect the serum proteins, the non-protein nitrogen, the chloride, and the haematocrit values of the blood. Unfortunately, in many of the cases, only two or three estimations were carried out and the conclusions to be drawn from these are naturally liable to be erroneous.

Cohen, Miller and Kramer [(40)] have demonstrated a fall in the blood non-protein nitrogen and the serum proteins as the result of continuous intra-venous injections of glucose and saline.

In the case of patient (a) (Table XXVI), in which several samples of blood were removed, there occurred a slight fall in both the proteins and the non-protein nitrogen as the result of the saline and glucose injections. These values remained within normal limits while the child was convalescing and did not rise to any extent before dismissal from the wards. In patient (c), although at first there occurred a marked fall in both the serum protein and the non-protein nitrogen values, this fall was only temporary and during the last week of the child's life both commenced to rise again even although large quantities of fluid were given. The number of stools passed during this period was not as great as occurred in some of the patients, as they averaged only about three per day. The increased concentration of the blood cannot therefore be wholly due to the number of loose stools, but suggests that either insufficient fluid had been administered to this patient or that there was inability of the blood or the tissues to hold water. Possibly transfusing this patient while the serum proteins were high adversely affected the prognosis, for it will be noted that both the serum proteins and the non-protein nitrogen, particularly the latter, continued to rise after the transfusion.

The non-protein nitrogen exhibited very high values, even with treatment, in all cases terminating fatally. In the case of patient (g), the non-protein nitrogen continued to rise

TABLE XXVI.

Variations in Blood after Saline and Glucose Injections.

	Name	Serum Protein gms. %	N.P.N. mgs.%	Injections	Date	
(a)	R.M.	7.65	47.1	120 c.c. glucose & saline I.V.	19/11/34	
	aet 5 months	7.26	39.3	120 c.c. " " "	20/11/34	
		6.34	31.7	120 c.c. " " "	21/11/34	
		4.96	32.2	120 c.c. " " "	22/11/34	
		7.00	33.3	—	23/11/34	
		6.47	39.5	120 c.c. glucose & saline I.V.	24/11/34	
		-	-	Transfused 75 c.c. Blood	28/11/34	
	Sent home well	7.33	24.5	120 c.c. glucose & saline I.V.	4/12/34	
		6.61	34.0	—	13/12/34	
(b)	D.L.	8.62	52.6	140 c.c. glucose & saline I.V.	7/3/35	
	aet 3 months. Died	7.46	58.3	200 c.c. saline I.P.	11/3/35	
(c)	J.M.	9.21	96.1	120 c.c. glucose & saline I.V.	24/11/34	
	aet 19 weeks	7.96	60.3	120 c.c. " " "	26/11/34	
		-	-	90 c.c. " " "	27/11/34	
		6.55	34.7	--	28/11/34	
		6.38	39.6	--	30/11/34	
		6.27	23.6	120 c.c. glucose & saline I.V.	4/12/34	46 stools
		7.26	29.8	45 c.c. " " "	8/12/34	
	Child worse.	8.62	57.4	120 c.c. " " "	12/12/34	
		-	-	120 c.c. Saline I.P. 120 c.c. " "	13/12/34	
		8.60	80.0	Transfused 80 c.c. Blood.	16/12/34	
	Died	8.86	94.3	Transfused 80 c.c. Blood.	17/12/34	

TABLE XXVI (Contd.)

Variations in Blood after Saline and Glucose Injections.

	Name	Serum Protein gms.%	N.P.N. mg.%	Chloride ccs. N/10 Cl	Haematocrit % R.B.C.	Haematocrit % Plasma	Injections	Date
(d)	D.T.	-	40.3	96.1	39.6	60.4	150 c.c. saline I.P.	12/5/35
	aet 15 weeks. Died.	6.57	96.3	101.1	33.3	66.6	150 c.c. " "	13/5/35
(e)	A.S.	10.03	73.5	83.6	29.6	70.4	120 c.c. glucose & saline I.P.	12/5/35
	aet 6 months Died	9.25	104.2	99.4	33.0	67.0	120 c.c. glucose & saline I.V.	13/5/35
(f)	B.I.	8.82	55.5	79.44	-	-	160 c.c. glucose & saline I.V.	5/9/35
	aet 11 months	8.72	44.6	83.8	-	-	120 c.c. " " "	6/9/35
	Died	8.06	-	88.4	-	-	120 c.c. " " "	7/9/35
(g)	J.O'H.	8.48	66.6	92.8	-	-	120 c.c. glucose & saline I.V.	10/9/35
	aet 30 weeks.	8.60	68.8	58.6	-	-	120 c.c. " " " 120 c.c. " " "	11/9/35
		9.98	131.5	-	-	-	200 c.c. saline I.P. 120 c.c. glucose & saline I.V.	12/9/35
	Died	6.59	147.0	105.1	-	-	120 c.c. " " " 200 c.c. saline I.P.	13/9/35
(h)	M.B.	8.46	90.6	74.9	-	-	100 c.c. glucose & saline I.V.	17/9/35
	aet 16 weeks.	8.00	96.4	92.88	-	-	100 c.c. " " "	18/9/35
	Sent home well.	9.03	-	-	-	-	120 c.c. " " "	19/9/35

despite the fact that apparently large and adequate quantities of fluid were administered by both the intra-peritoneal and intra-venous routes. It would thus appear that if an already high non-protein nitrogen continues to rise, in patients suffering from infantile diarrhoea, even after saline and glucose injections, the prognosis is bad. It is possible that, in these severe and acute cases, sufficient fluid had not been administered to rehydrate the tissue depots of the body and institute satisfactory renal function.

The plasma (haematocrit) volume % is given in two patients, (d) and (e). In one there was a fall and in the other a rise, even although both had received comparable amounts of fluid.

It is interesting to note that the blood chloride values in all patients examined ((d),(e),(f),(g) and (h)) showed a rise which appears more marked in (e),(f) and (g), as the result of saline and glucose injections. All these patients, with the exception of (h), died. It was noticed by Hartmann[21], that the blood of patients suffering from infantile diarrhoea and an associated acidosis, when treated with Ringer's solution and saline, developed a great increase of base-chloride at the expense of bicarbonate. As a result of this finding he has suggested that saline should not be administered to these cases because of the danger of chloride replacing bicarbonate and so increasing the acidosis already present. In this series of patients however no clinical evidence of an increase in acidosis was noted as the result of the saline and glucose injections. Views similar to those of Hartmann[21] have been expressed by Maizels and Smith[22] et alii[41], while McIntosh et alii[53] discovered in their series only one patient who showed the increase of base chloride at the expense of bicarbonate on which Hartmann has laid such stress. From these results it does appear as if an increased blood chloride follows saline and glucose administration and that the highest blood chloride values occur in the later stages of fatal cases.

(B). Water Distribution after Fluid Administration.

There at present exists much confusion in our ideas of the water and chloride re-distribution in both animals and human beings as the result of fluid administration. Greene and Rowntree[71] et alii [72] have shown that, when the volume of the fluid in the circulation of animals is increased by forced water administration, much of the extra fluid introduced escapes from the circulation with great rapidity, but very little is definitely known about the regulating mechanism. In saline infusion experiments on dogs, Adolph, Gerbasi and Lepore[73] demonstrated similar rapid losses of fluid and also observed that chloride left the circulation even more rapidly than water. This rapid loss of chloride has also been reported by Iversen and Hansborg[74] who even found a variation in the chloride content of the arterial and venous blood during the duration of saline infusion. On the other hand Davis[75], also using dogs as his experimental animals and plasma volume and haemoglobin as the index of dilution, found that the blood vascular system did act as a fluid reservoir, for he noted that the blood remained diluted for a period of 5 hours after the infusion. The maximum blood dilution was not reached for a period of one hour, the initial dilution being immediately followed by concentration and later by a further dilution. If the former investigators be correct, very small alterations in the blood constituents should be found after fluid administration.

(C). Variations in the Blood Constituents after Single Saline and Glucose Injections.

Normal Infants. The variations of the blood constituents were examined in normal infants for periods varying between three and five hours after the introduction of intra-venous saline or saline-and-glucose solutions.

Specimens of blood were removed (a) before injection
(b) ½ hour after "
(c) 1 " " "
(d) 2 hours " "
(e) 3 " " "

and in some cases when it was considered possible another specimen (f) was removed, between 4½ and 5 hours after the fluid administration.

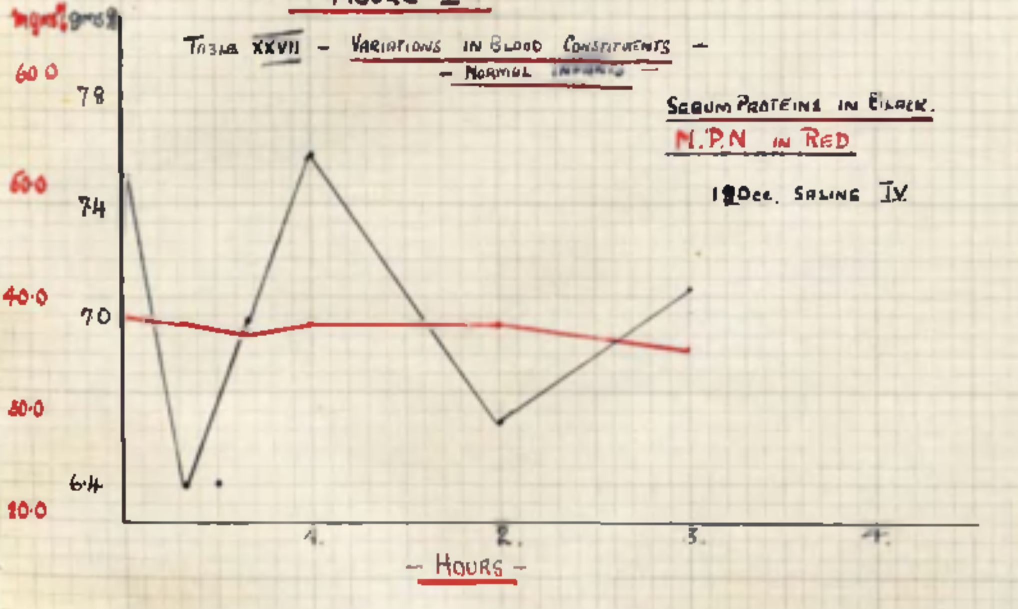
From the results (Tables XXVII to XXX; Figs. I-IV) it will be seen that the N.P.N. values showed a gradual fall in two cases, over the three-hour period during which they were examined.

TABLE XXVII

Effect of Parenteral Fluid - Normal Infant.

Name	Time	Serum Protein gms. %	Blood N.P.N. mgs.%	Remarks
(J.M.)	Before	7.51	38.2	
Hydrocephalus	20 min.	6.40	37.8	120 ccs.Saline
aet. 6 mths.	40 min.	6.98	36.5	Intra-Venously
	1 hr.	7.59	37.8	
	2 hrs.	6.63	37.3	
	3 hrs.	7.09	35.5	

FIGURE I

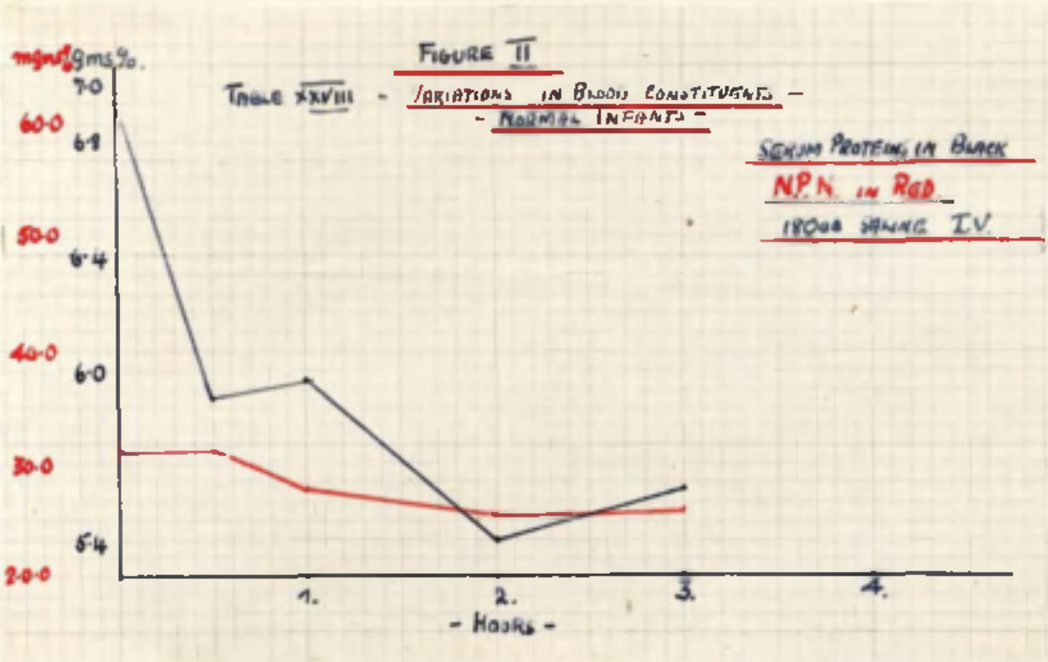


In one patient (J.G., Table XXVIII) where isotonic saline was used alone, the blood sugar values remained remarkably steady over the period of examination, while in another (C.S. Table XXX), where 10% glucose and saline had been used, the blood sugar naturally rose at first but had returned to practically the pre-infusion level after the interval of three hours.

TABLE XXVIII.

Effect of Parenteral Fluid - Normal Infant.

Name	Time	Serum Protein gms. %	Blood N.P.N mgs.%	Blood Sugar mgs.%	Remarks
(J.G.)	Before	6.92	30.7	68.7	
Hydrocephalus	½ hr.	5.92	30.9	69.2	180 ccs. Saline Intra-venously
aet. 20 wks.	1 hr.	5.96	27.6	76.3	
	2 hrs.	5.40	25.2	66.1	
	3 hrs.	5.58	25.5	63.7	



The total serum proteins however had rather characteristic and remarkable variations, more marked in some cases (Tables XXVII, XXIX and XXX) than in others. Half an hour after the injection the proteins show a definite and significant fall which most probably would have been still lower if specimens had been removed immediately after completing the saline injection - (see Table XXVII in which the reading at 20 minutes was very much lower than that at 40 minutes). After the lapse of one hour the values had risen in most cases to very near the pre-infusion level and in several cases (Tables XXVII, XXIX and XXX) were above this level. At 2 hours the value had dropped, this fall being more marked in some cases than in others, while at three hours the value again showed a rise in all cases (Figs. I-IV).

TABLE XXIX.

Effect of Parenteral Fluid - Normal Infant.

Name	Time	Serum Protein gms. %	Remarks
(J.N.)	Before	6.45	60 ccs. glucose 10% & saline.
Tuberous Sclerosis.	½ hr.	6.03	Intra-venously.
aet.6 mths.	1 hr.	6.55	
	2 hrs.	6.00	
	3 hrs.	6.18	

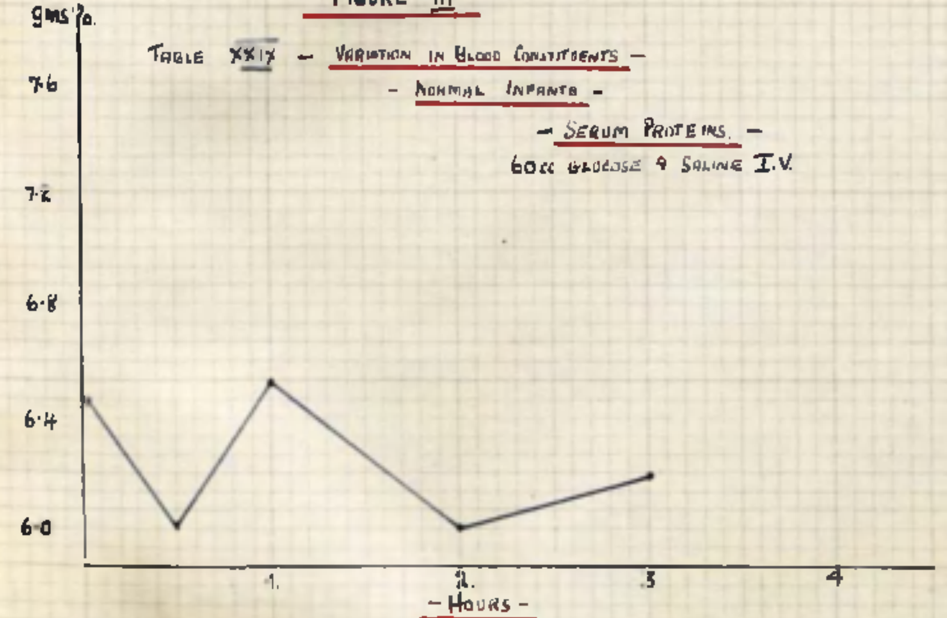


FIGURE III

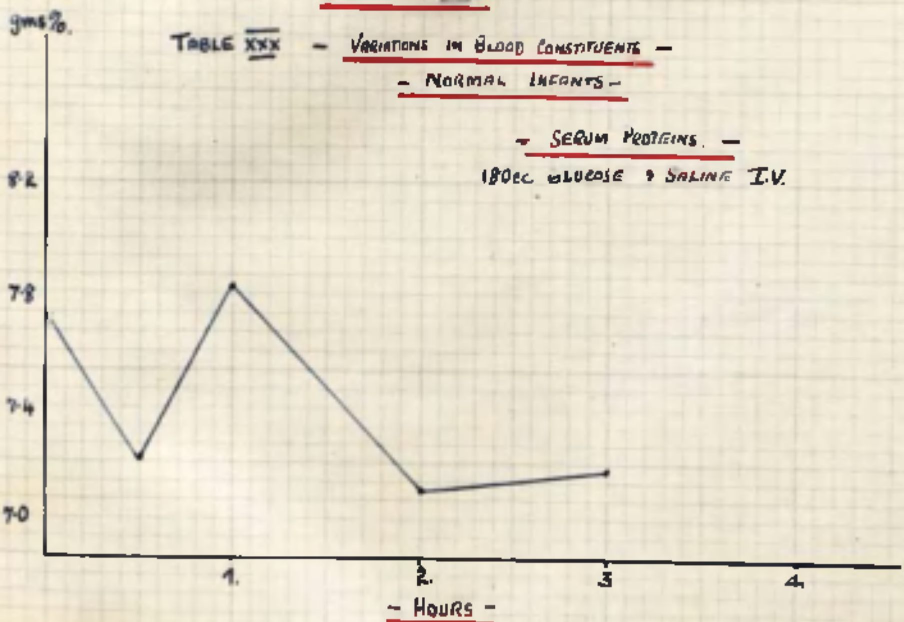
TABLE XXIX - VARIATION IN BLOOD CONSTITUENTS -
- NORMAL INFANTS -
- SERUM PROTEINS. -
60cc GLUCOSE & SALINE I.V.

TABLE XXX.

Effect of Parenteral Fluid - Normal Infant.

Name	Time	Serum Protein gms. %	Blood Sugar mgs.%	Remarks
(C.S.)	Before	7.74	82.0	180 ccs. glucose & saline I.V.
(Osteitis)	½ hr.	7.22	347.8	
aet 1 yr.	1 hr.	7.83	268.7	
	2 hrs.	7.11	116.9	
	3 hrs.	7.17	85.9	

FIGURE IV



It also appears probable that if specimens had been removed after the lapse of 4-5 hours the serum protein value would have shown a reading very near that of the pre-infusion value (see Table XLVIII, in which specimens were removed up to a period of 5 hours after infusion).

These alterations in the serum protein values over such a short interval can only be explained by (1) alternations of fluid between the circulation and the tissue spaces or, until the end of three hours when (2) possibly renal action comes into play and the excess fluid is excreted.

Miller and Pointdexter[43] have also demonstrated that in dogs the serum proteins fell immediately after saline injections, commenced rising after 15 minutes, but did not reach the pre-injection level at the end of one hour (Table XXXI).

TABLE XXXI.

Serum Proteins Before and After Saline Injections (Dogs).

After Miller and Pointdexter[43].

Before	Immediately after.	15 min. after	60 min. after
7.30 gms.%	4.30 gms.%	5.6 gms.%	5.6 gms.%

Very similar findings are reported by Onozaki[76] (Table XXXII) who studied the serum protein values of rabbits for a period of seven hours after the intra-venous injections of isotonic saline. He found that the serum protein value usually fell

TABLE XXXII.

Serum Proteins Before and After saline Injections (Rabbits).

After Onozaki[76]
In gms.%

	Before	After 5 min.	½ hr.	1 hr.	2 hrs.	3 hrs.	5 hrs.	7 hrs.
Rabbit I	6.57	5.80	6.42	6.43	6.25	6.37	6.31	6.25
Rabbit II	5.51	4.86	4.90	5.66	5.45	5.30	5.19	5.12

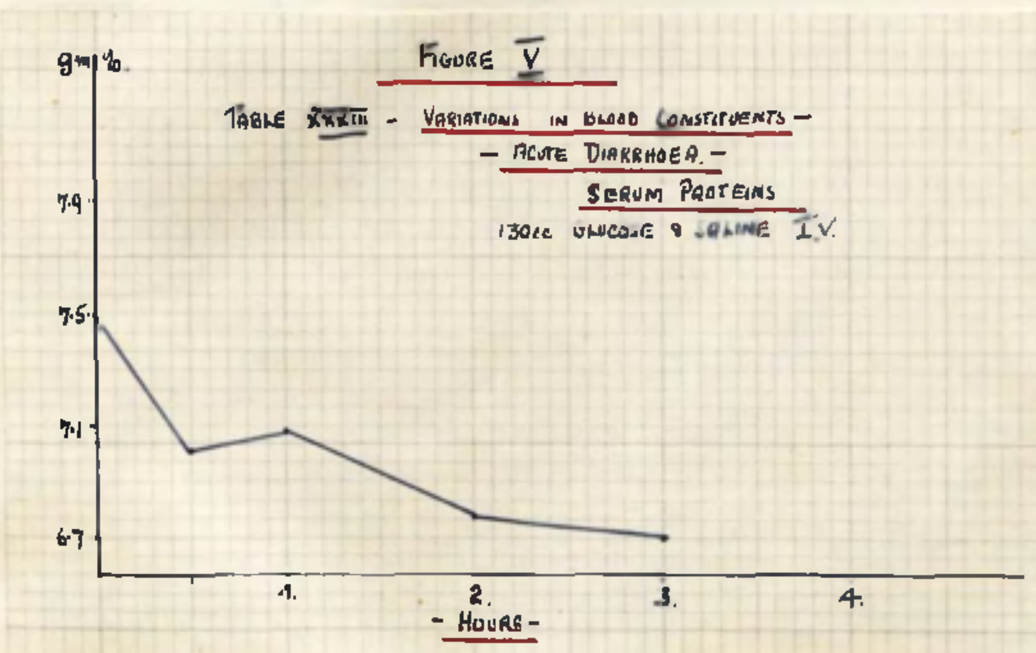
immediately after the injection, commenced rising at once and attained a value slightly lower than the pre-injection figure at the end of one hour, after which they again fell and did not quite reach the pre-injection value at the end of seven hours. He also mentions that similar findings were noted when the haemaglobin values of the blood in rabbits were studied after saline injections. The variations of the serum proteins in this series of normal infants after saline and glucose injections are very similar to the findings of the last mentioned investigator in the case of animals and are due most likely to fluctuations of the total plasma volume.

Acute Infantile Diarrhoea Patients. During a careful search of the literature no reference to the water distribution after intra-venous isotonic injections in patients with infantile diarrhoea could be found. In dogs suffering from the effects of dehydration, however, Davis[75] has shown that there is a greater ability on the part of the blood to hold both isotonic saline and glucose than occurs in normal animals.

TABLE XXXIII.

Effect of Parenteral Fluid - Acute Diarrhoea.

Name	Serum Protein gms. %	Time	Remarks
M.McL.	7.48	Before	130 c.c. 10% glucose & saline
	7.02	½ hr.	Intra-venously.
	7.09	1 hr.	
	6.77	2 hrs.	(Child acutely ill)
	6.70	3 hrs.	(B.P. 55 mgs. Mercury)



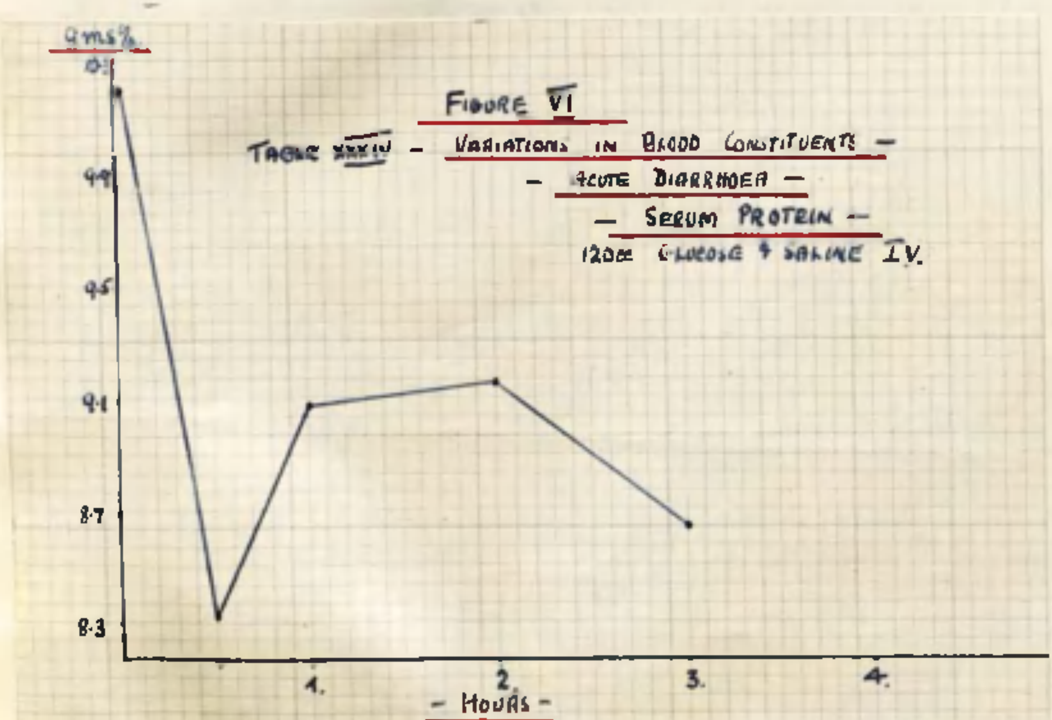
In patients suffering from acute infantile diarrhoea, in which the blood was examined for a period of three hours after fluid injections, the non-protein nitrogen values did not show any marked fall and in only one case (Table XXXVI) did this fall amount to as much as 8 mgs. %.

The blood sugar variations were somewhat similar to those in normal infants to whom 10% glucose and saline had been

TABLE XXXIV.

Effect of Parenteral Fluid - Acute Diarrhoea.

Name	Time	Serum Protein gms. %	Remarks.
(I.M.) aet $1\frac{3}{12}$ yrs.	Before	10.19	120 c.cs. 10% glucose & saline Intra-venously.
	½ hr.	8.32	
	1 hr.	9.07	
	2 hrs.	9.14	(Child very dehydrated)
	3 hrs.	8.64	

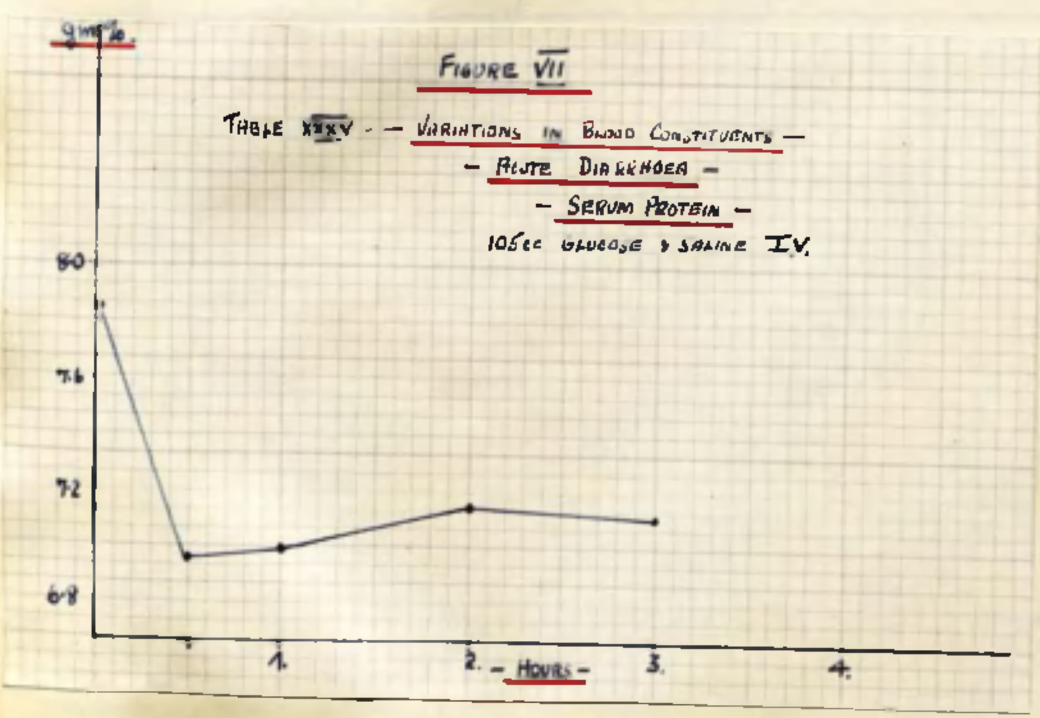


given, but it is rather interesting to observe that the value in one case (Table XXXVI), at the end of three hours, was higher than before the injection.

TABLE XXXV.

Effect of Parenteral Fluid - Acute Diarrhoea.

Name	Time	Serum Protein gms.%	Remarks.
(V.F.) aet 22 wks.	Before	7.85	105 c.cs. 10% glucose & saline
	½ hr.	6.96	Intra-venously.
	1 hr.	6.98	
	2 hrs.	7.15	(Acutely ill)
	3 hrs.	7.12	



On studying the serum protein values throughout the three-hour period after injection it is noticeable that although the initial fall immediately after injection may be just as marked as in the case of the normal infants, yet the secondary fall, if it does occur, is usually delayed until the third hour (Tables XXXIV to XXXVII, Figs. VI to X). The variations of serum protein in many of these patients are also less marked

TABLE XXXVI.

Effect of Parenteral Fluid - Acute Diarrhoea.

Name	Time	Serum Protein gms.%	Blood N.P.N.	Blood Sugar	Remarks
			mgs.%		
(A.J.) aet $1\frac{5}{12}$ yrs.	Before	8.91	67.5	123.8	220 c.cs.10% glucose & saline Intra-venously.
	$\frac{1}{2}$ hr.	7.65	57.4	877.7	
	1 hr.	8.71	64.1	625.0	
	2 hrs.	8.56	59.5	388.3	(Severe dehydration)
	3 hrs.	8.62	58.8	198.0	

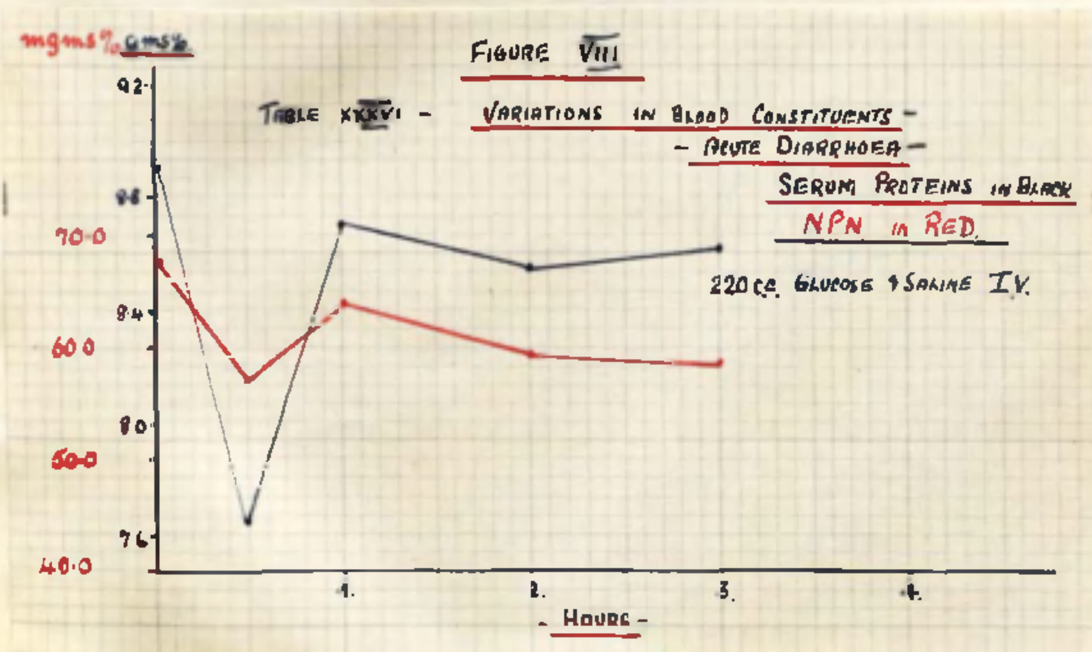
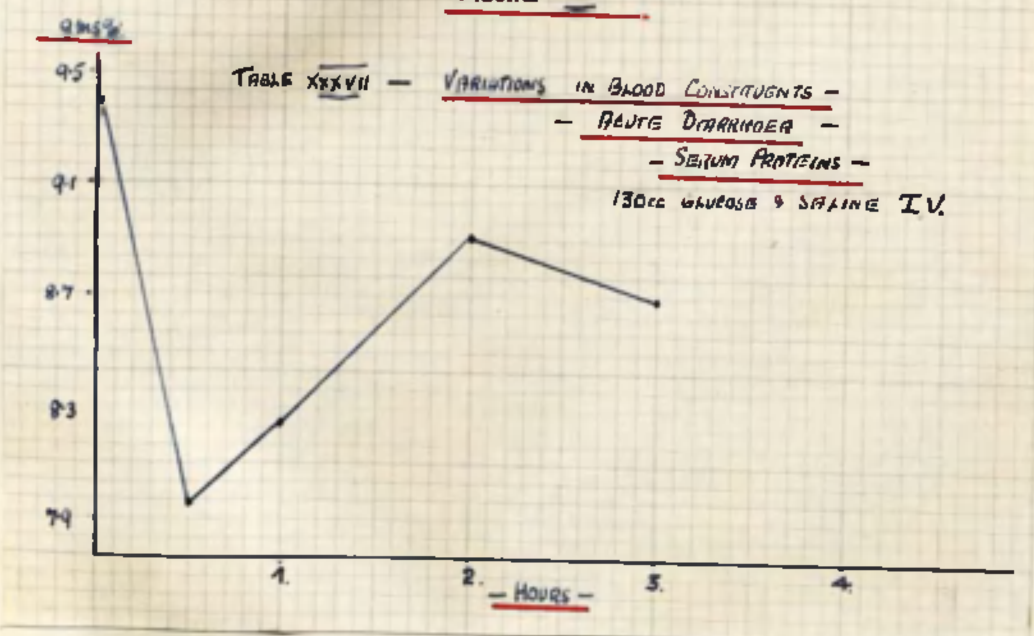


TABLE XXXVII.

Effect of Parenteral Fluid - Acute Diarrhoea.

Name	Time	Serum Protein gms.%	Remarks
(H.McN.) aet 32 wks.	Before	9.39	130 c.cs.10% glucose & saline Intra-venously
	½ hr.	7.96	
	1 hr.	8.26	
	2 hrs.	8.91	(Severe Dehydration)
	3 hrs.	8.69	

FIGURE IX



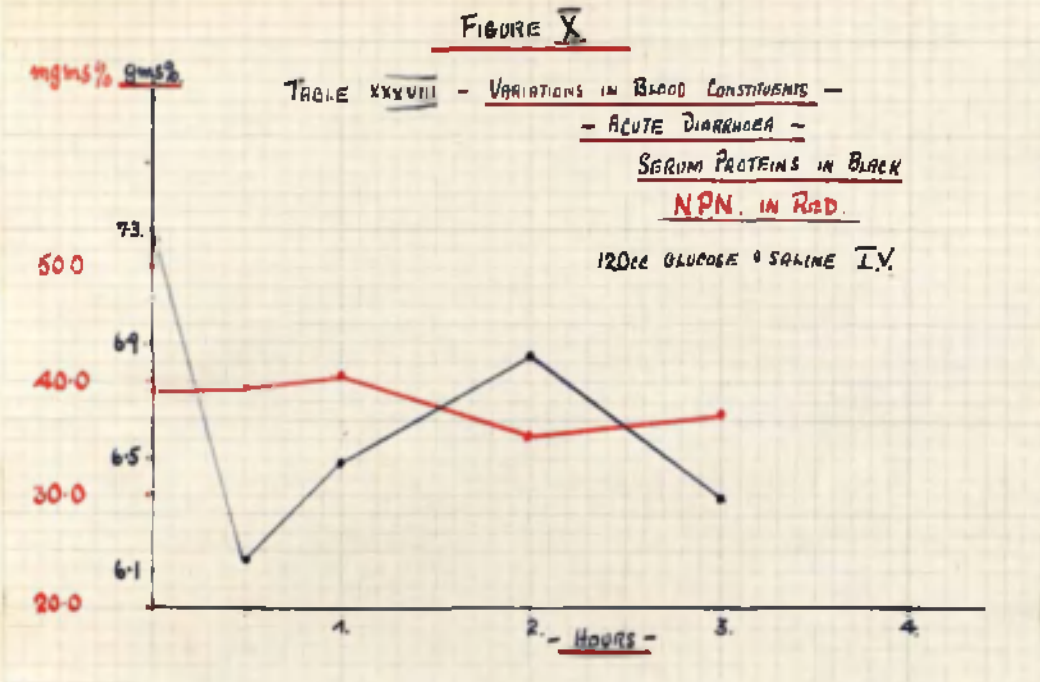
than those found in a group of normal infants under similar experimental conditions. In the case of patient A.J. (Table XXXVI) however the secondary fall in serum protein occurs earlier than in the other cases.

Since the serum proteins serve as an index of plasma volume concentration it must be accepted that in these acute infantile diarrhoea patients the blood plasma remains diluted for a longer period than in normal cases, the secondary serum protein fall occurring at 3 hours instead of 2 hours as in normals.

TABLE XXXVIII.

Effect of Parenteral Fluid - Acute Diarrhoea.

Name	Time	Serum Protein gms.%	Blood N.P.N. mgs.%	Blood Sugar mgs.%	Remarks
(R.M.)	Before	7.26	39.3	91.3	120 c.cs.10% glucose & saline
aet 15 weeks.	½ hr.	6.14	39,7	666.8	Intra-venously
	1 hr.	6.49	40.3	540.1	
	2 hrs.	6.85	35.2	322.0	(Severe dehydration)
	3 hrs.	6.36	37.3	-	



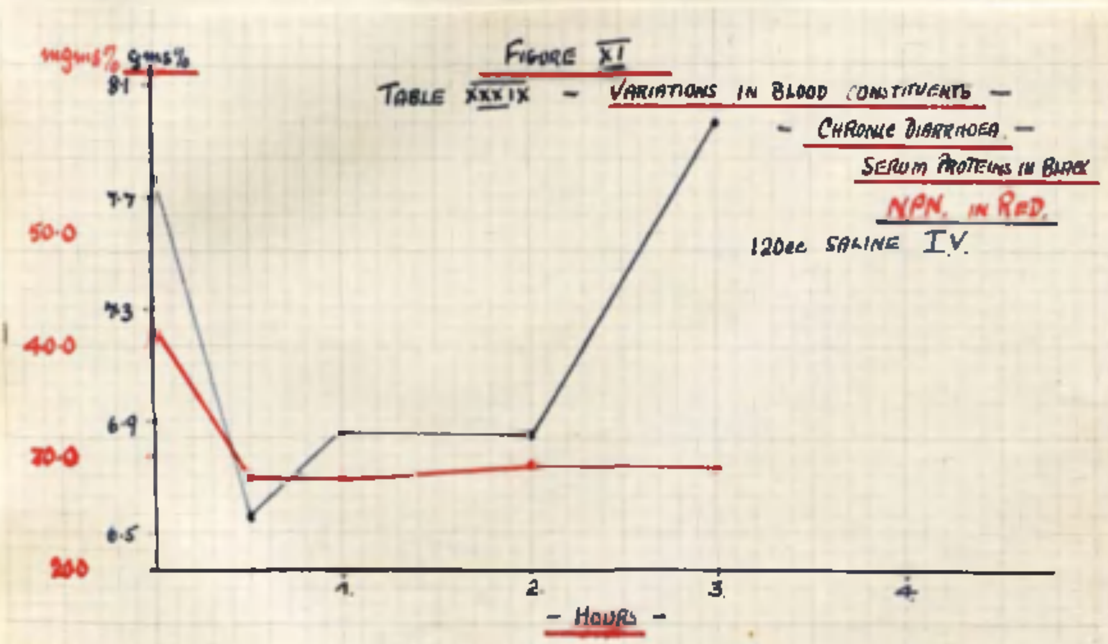
The blood pressure, according to Blalock, Beard and Theiss[77] and Adolph and Lepore[78], plays an important part in the re-distribution of fluids and solids during saline injections in animals. The latter investigators discovered that more fluid passed into the tissue spaces as the result of a high arterial blood pressure than occurred when the mean arterial pressure was low. It is possible that the slow passage of fluid from the circulation in cases of acute infantile diarrhoea may be due to a diminished blood pressure, although Hill[79] maintains that there is no diminution of the blood pressure in these infants. Attempts were made to estimate the blood pressure in several of these infants but in only one (M.McL. Table XXXIII) was this successfully accomplished, and in this case the reading appeared to be low.

<u>Chronic Infantile Diarrhoea Patients.</u> In a consideration of patients with chronic infantile diarrhoea (Tables XXXIX to XLVI, Figs. XI to XVIII) who have had their blood examined

TABLE XXXIX.

Effect of Parenteral Fluid - Chronic Diarrhoea.

Name	Time	Serum Protein gms. %	Blood N.P.N. mgs.%	Remarks
(W.A.) aet 45 wks.	Before	7.78	41.3	120 c.cs. Saline
	½ hr.	6.55	28.5	Intra-venously
	1 hr.	6.85	28.7	
	2 hrs.	6.83	29.4	(Child not acutely ill)
	3 hrs.	7.96	29.0	(% expected Wt. 74)

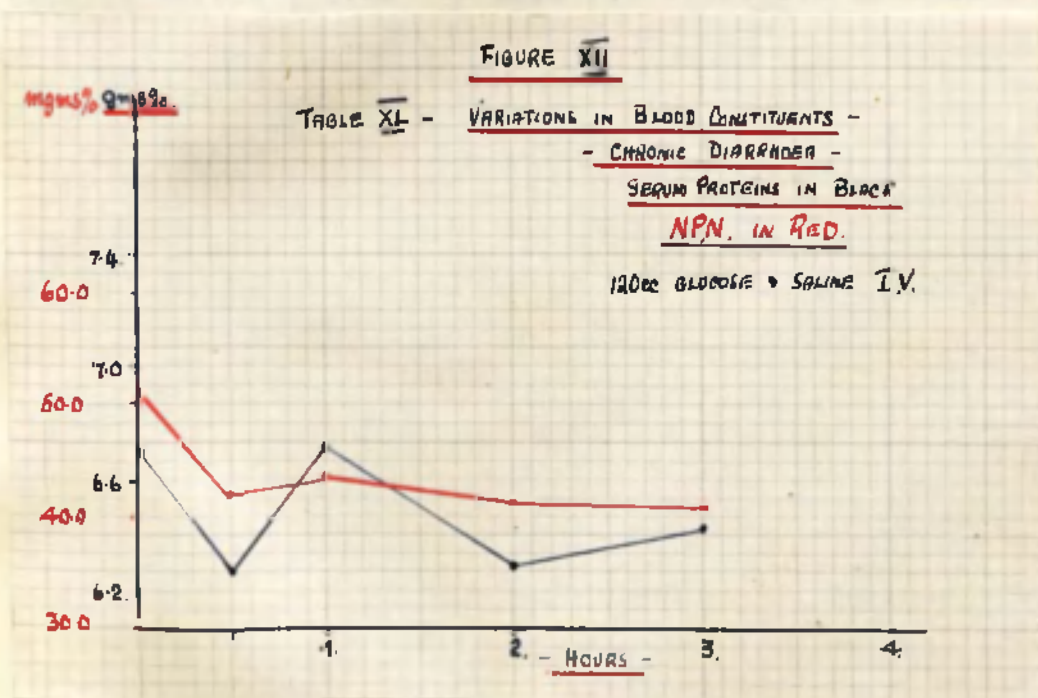


under similar experimental conditions, the non-protein nitrogen values in all cases except one showed a definite fall during the period of observation. The exception to this finding was C.D. (Table XLII, Fig.XIV), whose non-protein nitrogen, low at the commencement, remained at a constant level during the three hourly period after saline injection.

TABLE XL.

Effect of Parenteral Fluid - Chronic Diarrhoea.

Name	Time	Serum Protein gms.%	Blood N.P.N. mgs.%	Remarks
(A.M.) aet 15 wks.	Before	6.70	51.0	120 c.cs.10% glucose & saline Intra-venously
	½ hr.	6.27	42.0	
	1 hr.	6.72	43.5	
	2 hrs	6.29	41.7	(Slight dehydration)
	3 hrs	6.42	40.9	(% Expected Wt. 83)

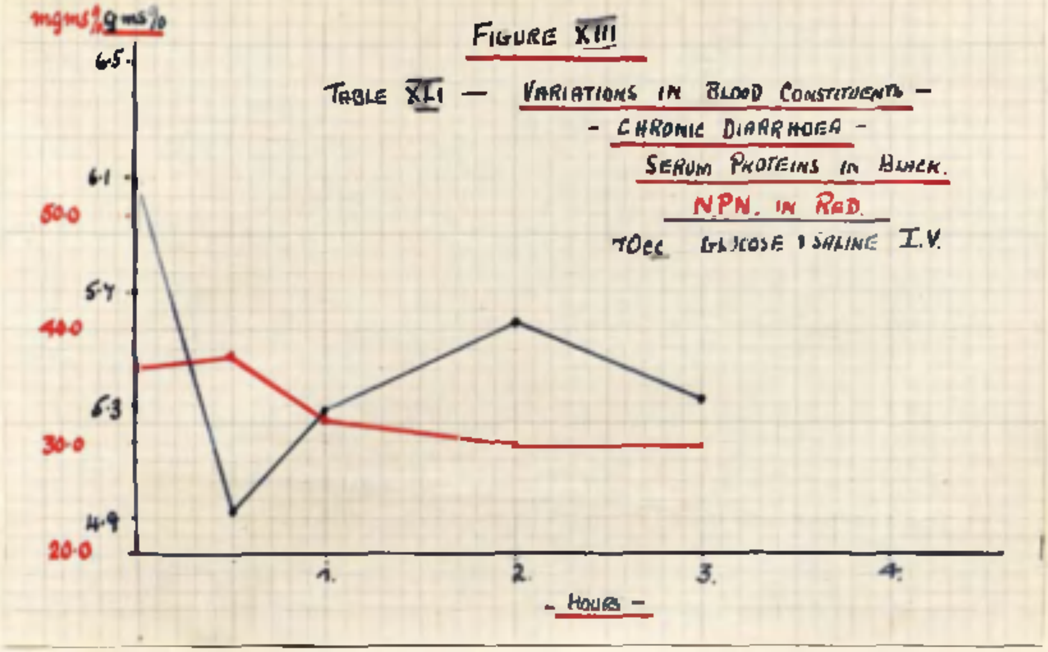


The blood sugar variations were followed in two patients. In one (Table XLII), to whom saline alone was given, very constant readings were found, while in the other (Table XLIII), to whom 10% glucose and saline was given, the blood sugar value at the end of three hours was even lower than the reading for the initial blood specimen.

TABLE XLI.

Effect of Parenteral Fluid - Chronic Diarrhoea.

Name	Time	Serum Protein gms.%	Blood N.P.N. mgs.%	Remarks.
(P.H.) aet 8 wks.	Before	6.09	36.8	70 c.cs. 10% glucose & saline
	½ hr.	4.92	37.8	Intra-venously.
	1 hr.	5.29	32.7	
	2 hrs.	5.60	29.9	(Not acutely ill)
	3 hrs.	5.38	29.8	(% Expected Wt. 44)



It thus appears that glucose administered to this type of patient by the intra-venous route is metabolised as well as is the case in normal infants. Similar views have been expressed by Levine, Wilson et alii (80)(81).

The serum protein variations are not at all characteristic. Some patients (Tables XL, XLII and XLVI) exhibit variations somewhat similar to those found in normal infants, but with very much smaller alterations in their respective values at the various times; another (Table XLI, Fig.XIII) shows variations somewhat similar to those found in acute cases; while the remainder show very variable and rather confusing combinations of these two main types (Tables XXXIX, XLIII and XLIV).

TABLE XLII.

Effect of Parenteral Fluid - Chronic Diarrhoea.

Name	Time	Serum Protein gms.%	Blood N.P.N. mgs.%	Blood Sugar mgs.%	Remarks
(C.D.)	Before	4.92	27.7	60.9	75 c.cs. Saline
aet 8 wks.	½ hr	4.54	29.1	60.2	Intra-venously
	1 hr.	4.84	27.5	57.2	
	2 hrs.	4.50	27.4	56.8	(Not acutely ill)
	3 hrs.	4.48	27.6	58.5	Pyuria

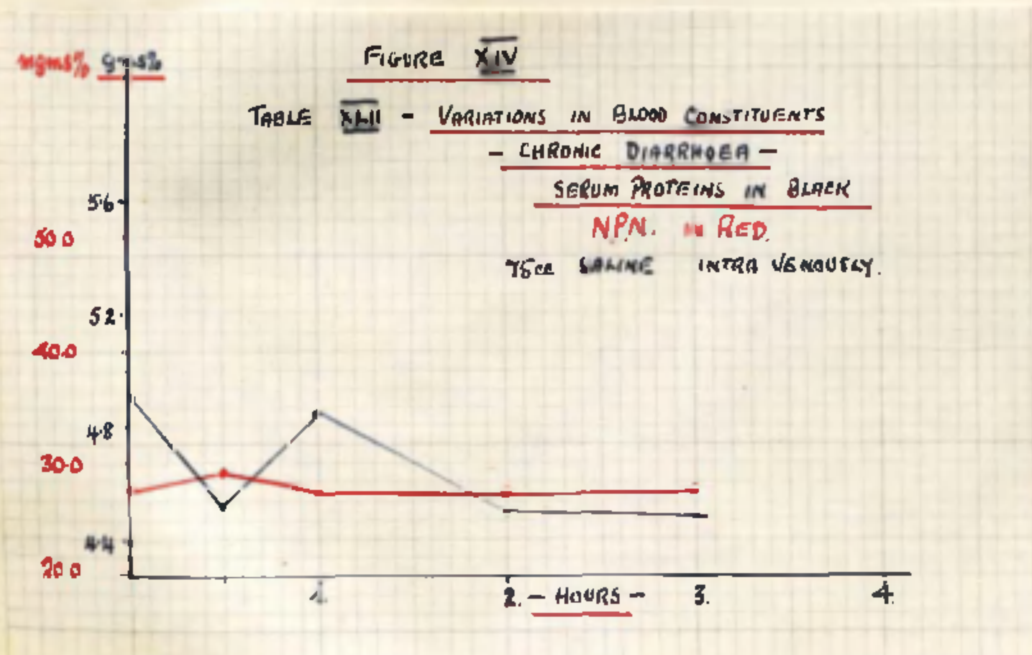


TABLE XLIII.

Effect of Parenteral Fluid - Chronic Diarrhoea.

Name	Time	Serum Protein gms.%	Blood N.P.N. mgs.%	Blood Sugar mgs.%	Remarks.
(A.H.)	Before	6.49	56.9	55.6	80 c.cs.10% glucose & saline
aet 11	½ hr.	5.79	49.0	400.0	Intra-venously
wks.	1 hr.	5.64	45.0	300.0	
	2 hrs.	5.36	47.6	138.9	
	3 hrs.	5.53	42.7	40.98	% Expected Wt. 50.

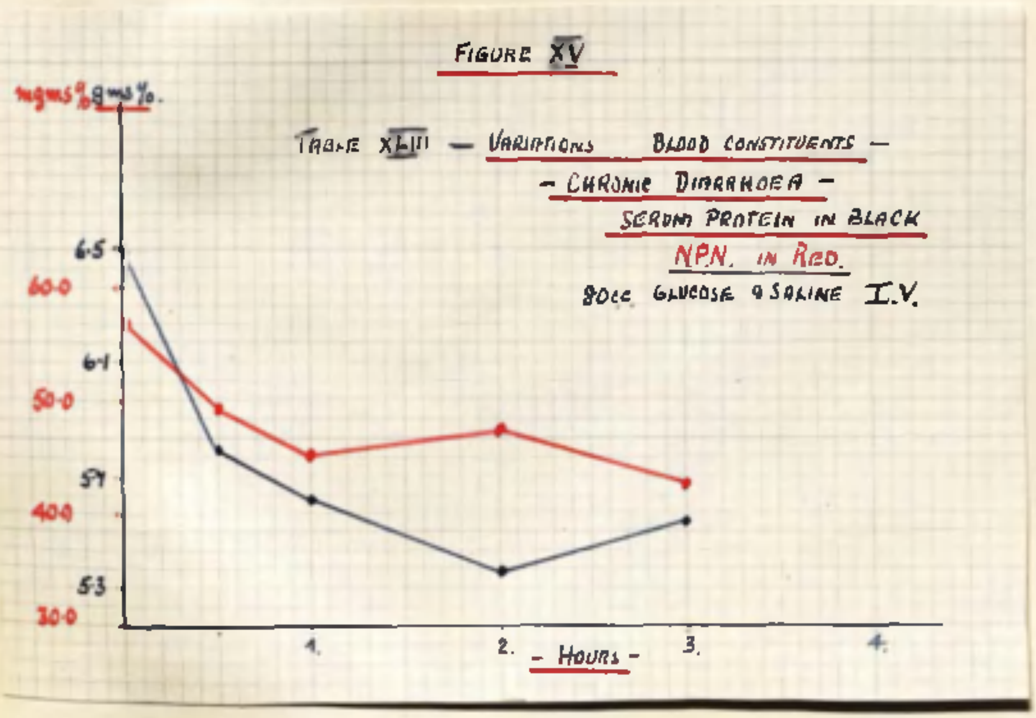


TABLE XLIV.

Effect of Parenteral Fluid - Chronic Diarrhoea.

Name	Time	Serum Protein gms.%	Remarks
(W.McF.) aet 3 wks.	Before	7.53	75 c.cs.10% glucose & saline Intra-venously (Not acutely ill)
	½ hr.	6.96	
	1 hr.	8.05	
	2 hrs.	7.17	
	3 hrs.	6.85	

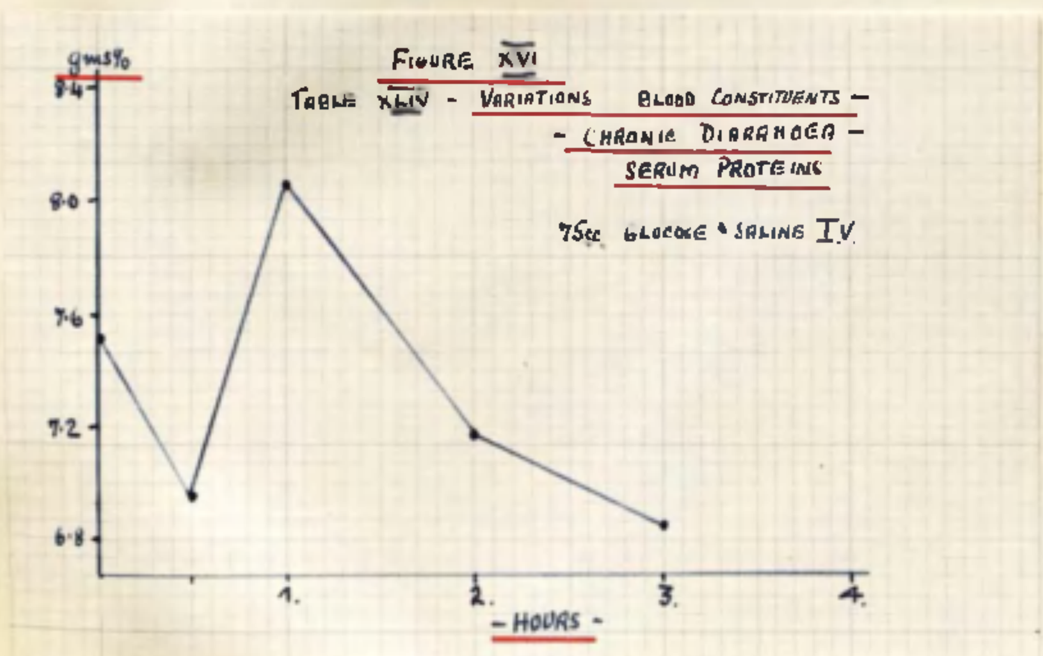
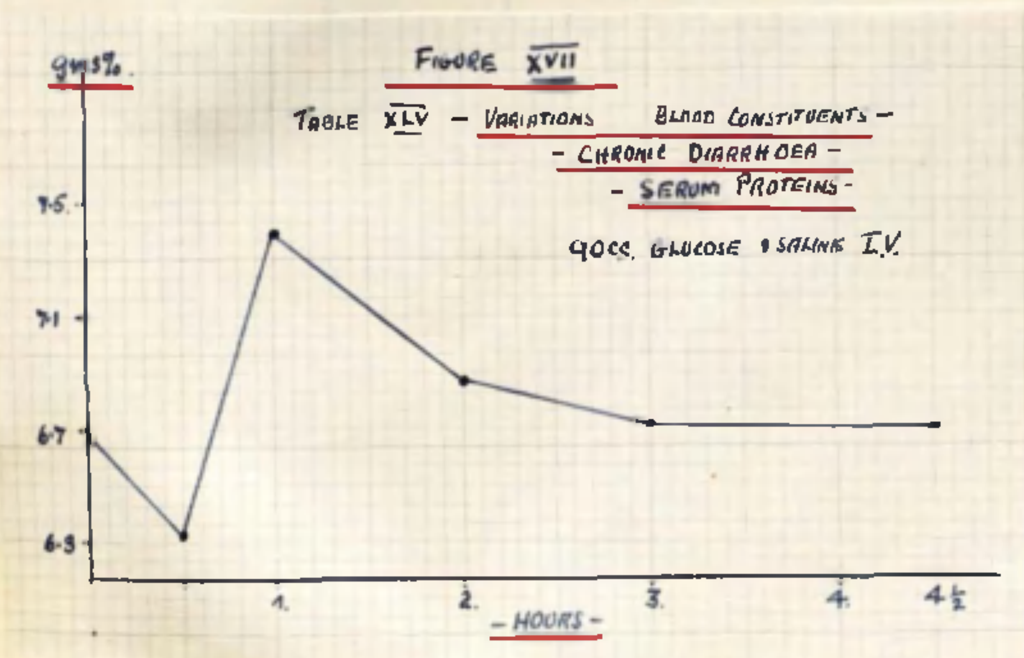


TABLE XLV.

Effect of Parenteral Fluid - Chronic Diarrhoea.

Name	Time	Serum Protein gms.%	Remarks
(M.McI.)	Before	6.68	90 c.cs.10% glucose & saline
aet 30 weeks.	½ hr.	6.34	Intra-venously
	1 hr.	7.39	
	2 hrs.	6.88	
	3 hrs.	6.72	(Not acutely ill)
	4½ hrs.	6.70	

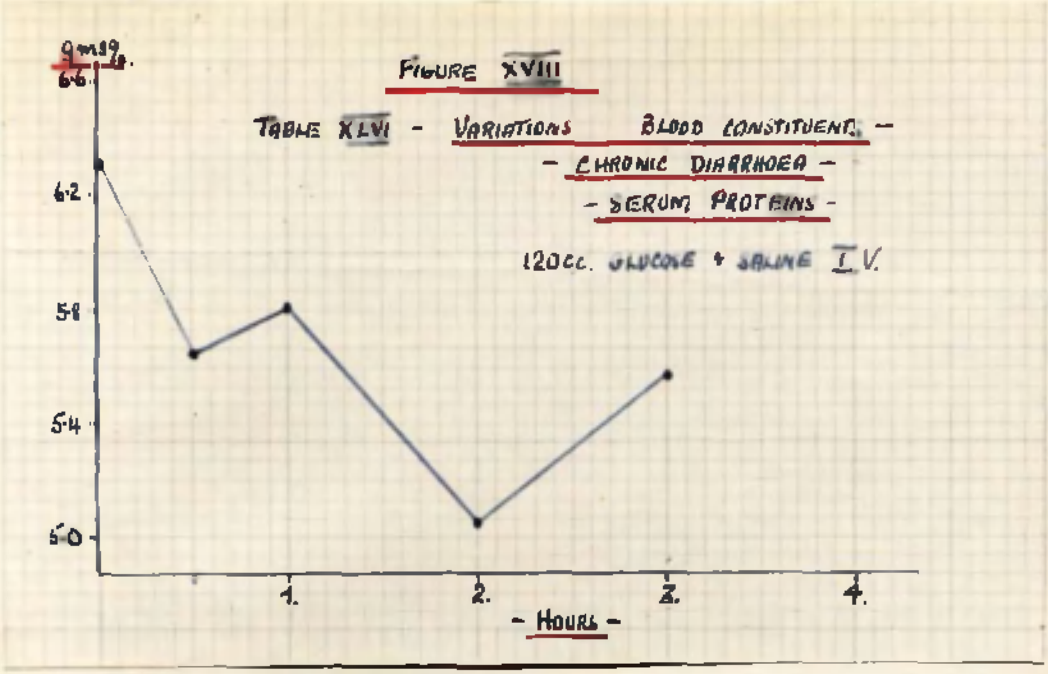


In the case of M.McI. (Table XLV), very peculiar serum protein values were found. As usual at 30 minutes there occurred a fall, which however was not marked, but at one hour the value became very much higher than that found before the commencement of the injection, gradually declining thereafter until at 4½ hours the value had almost regained the pre-infusion reading (Fig. XVII). It would thus appear that, in this case, the movements of fluid from the circulation were even more rapid and more marked than in the case of normal infants.

TABLE XLVI.

Effect of Parenteral fluid - Chronic Diarrhoea.

Name	Time	Serum Protein gms.%	Remarks.
(B.M.)	Before	6.29	120 c.cs. 10% glucose & saline
aet	½ hr.	5.65	Intra-venously
12 wks.	1 hr.	5.81	
	2 hrs.	5.05	
	3 hrs.	5.58	



(D). Water Distribution as judged by Serum Protein Alterations after Calcium Gluconate and Fluid Injections.

(a) Normal Infants. The rationale of calcium therapy is largely based on the alleged ability of the substance to decrease vascular permeability, allay nervous irritability, contract the peripheral capillaries and raise the blood pressure.

Any such action would be of great practical value in the treatment of acute infantile diarrhoea, especially in reducing vascular permeability. The present section of this enquiry was directed towards an exploration of this possibility in normal and diarrhoeal cases, but in view of the unknown sequelae of such treatment some difficulty was experienced in finding "normal" controls. Ultimately non-diarrhoeal patients who were otherwise likely to benefit from Ca therapy had to be taken as "normal" for this purpose.

TABLE XLVII.

Serum Protein after Calcium Gluconate - Normal Infant.

Name	Time	Serum Protein gms.%	Remarks
(C.S.)	Before	7.35	150 c.cs. 10% glucose & saline &
aet 26	½ hr.	6.47	10 c.cs. 10% Calcium Gluconate.
wks.	1 hr.	6.63	Intra-venously
(Tetany)	2 hrs.	6.34	
	3 hrs.	6.68	

Administration of calcium to normal infants should have the effect of decreasing the fluid movements between the circulation and the tissues, as shown by minimising the fluctuations of serum protein after injections.

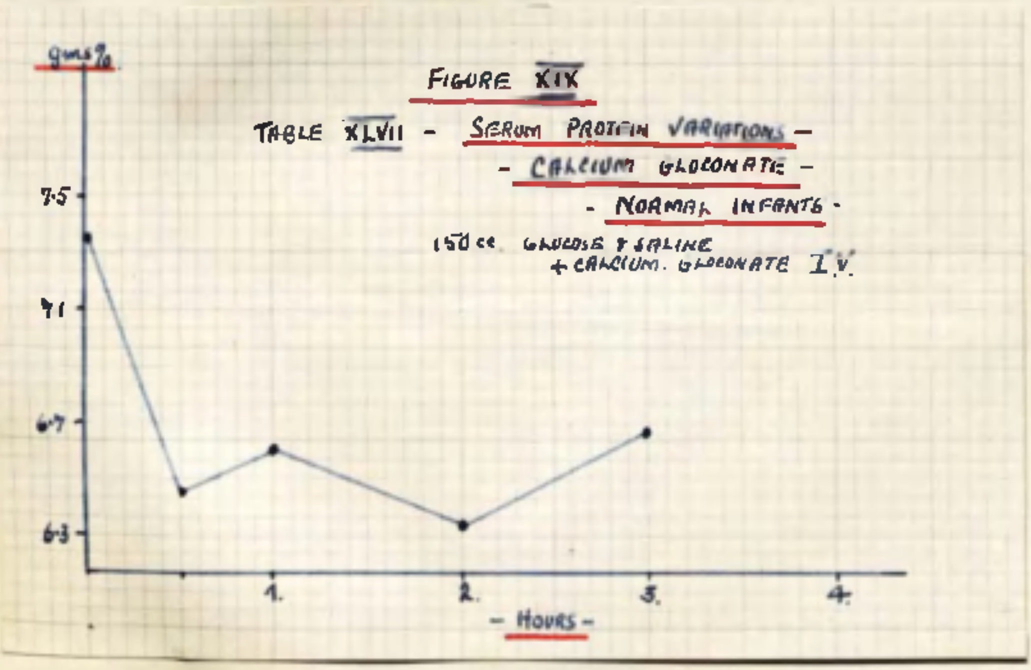
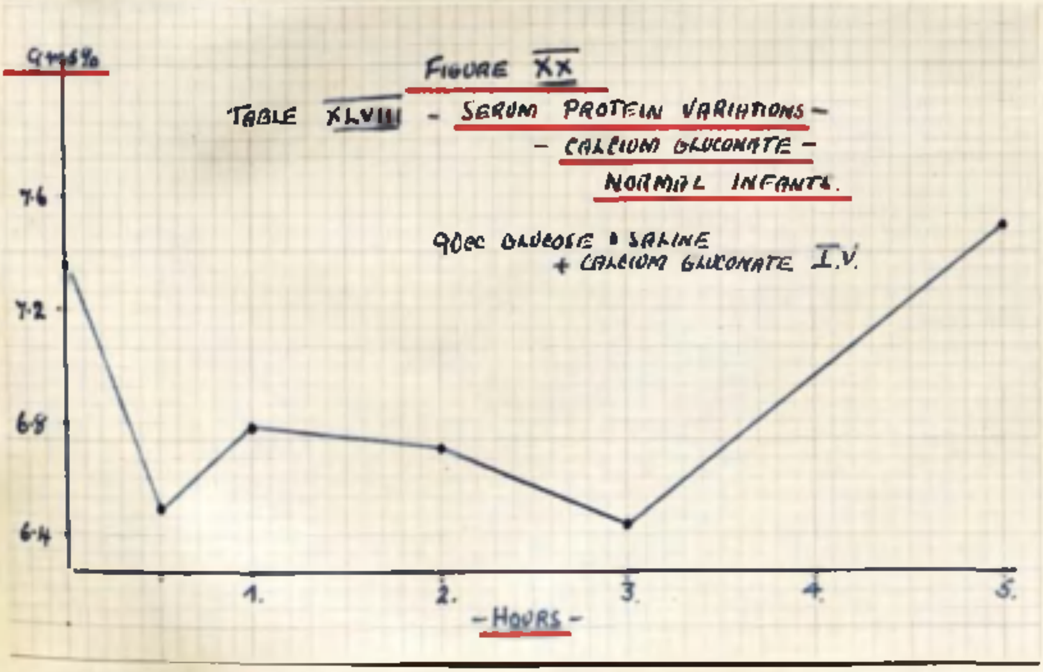


TABLE XLVIII.

Serum Protein after Calcium Gluconate - Normal Infant.

Name	Time	Serum Protein gms.%	Remarks
(C.S.)	Before	7.35	90 c.cs. 10% Glucose, saline and 8 c.cs 10% calcium gluconate
aet 26 wks.	½ hr.	6.51	Intra-venously
	1 hr.	6.79	
	2 hrs.	6.70	
	3 hrs.	6.42	
	5 hrs.	7.50	

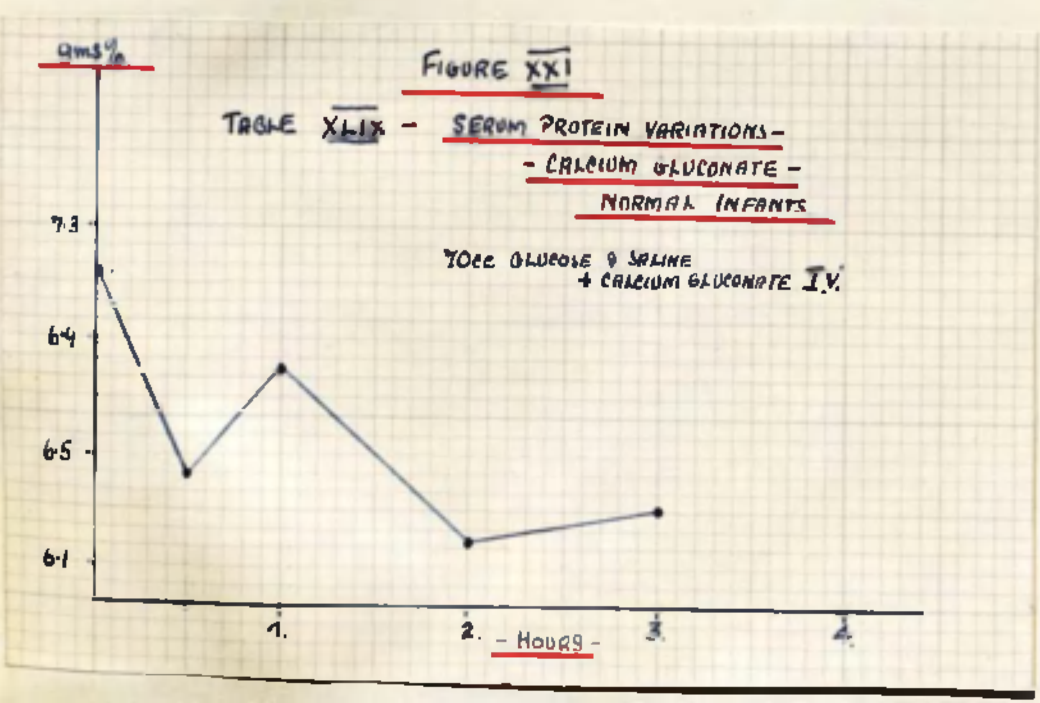


From an examination of the results (Tables XLVII to L) it will be noticed that in the case of two patients (Tables XLVII and XLVIII, Figs. XIX and XX) the variations of serum protein were very much less marked, after the initial fall, than was the case in normal infants to whom only glucose and saline had been administered (Figs. I and II).

TABLE XLIX.

Serum Protein after Calcium Gluconate - Normal Infant.

Name	Time	Serum Protein gms.%	Remarks
(J.N.) aet $\frac{6}{12}$ yrs. (Tuberous Sclerosis.)	Before	7.13	70 c.cs. 10% glucose, saline and 8 c.cs. 10% calcium gluconate. Intra-venously
	$\frac{1}{2}$ hr.	6.42	
	1 hr.	6.79	
	2 hrs.	6.18	
	3 hrs.	6.29	

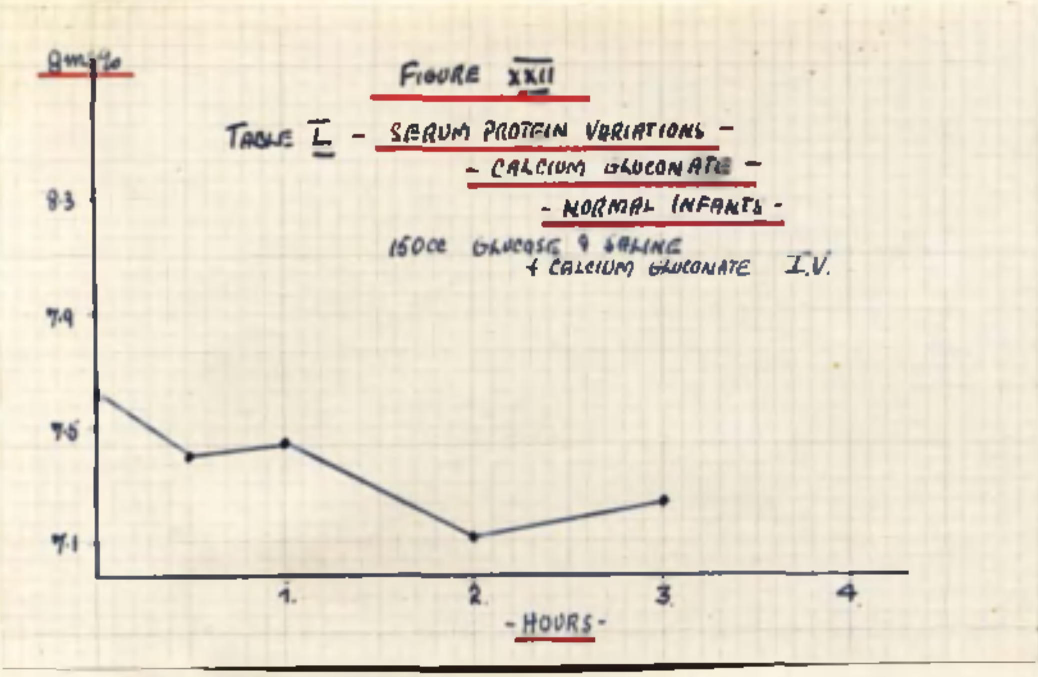


Similarly in the case of one infant (C.S. Tables XXX and L), to which nearly equal amounts of glucose and saline with and without calcium gluconate respectively were administered, the variations following calcium injection were very much less marked than with fluid alone. In another (J.N. Tables XXIX and XLIX) however, treated with calcium gluconate, the variations of serum protein after the initial fall are very similar to those found when only glucose and saline had been given. These findings suggest that, in most of the normal infants, the fluid movements between the circulation and (probably) the tissue spaces are reduced as the result of adding calcium gluconate to the saline and glucose injections.

TABLE L.

Serum Protein after Calcium Gluconate - Normal Infant.

Name	Time	Serum Protein gms.%	Remarks
(C.S.)	Before	7.65	150 c.cs.10% glucose & saline and 8 c.cs.10% calcium gluconate
aet 1 yr.	½ hr.	7.39	Intra-venously.
	1 hr.	7.44	
Syphilis	2 hrs.	7.11	
	3 hrs.	7.24	

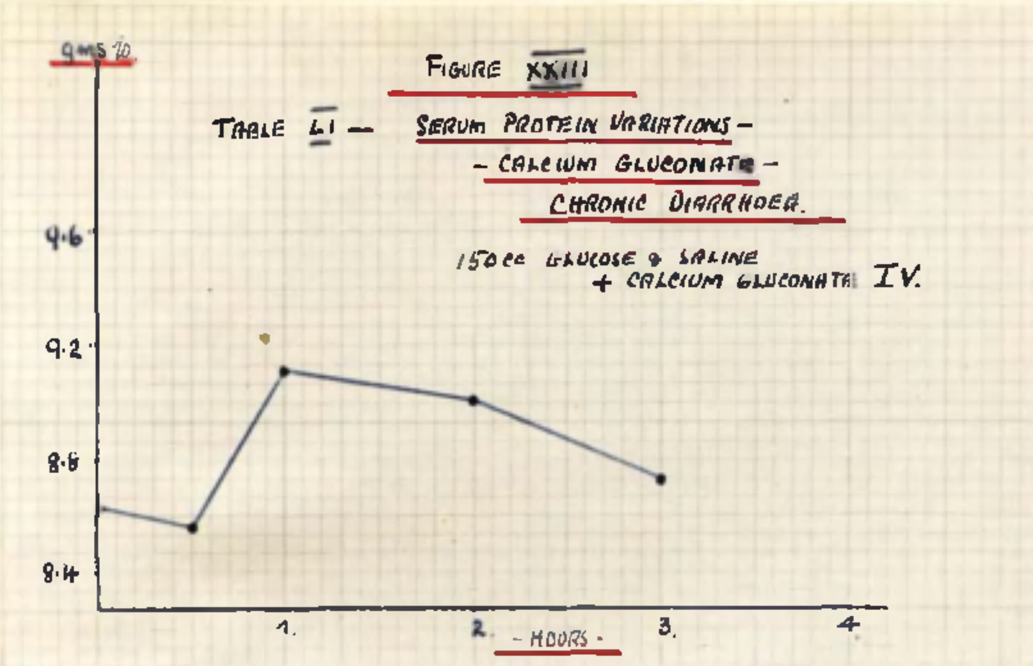


(b) Acute and Chronic Infantile Diarrhoea.

TABLE LI.

Serum Protein after Calcium Gluconate - Diarrhoea.

Name	Time	Serum Protein gms.%	Remarks
(C.B.)	Before	8.62	150 c.cs.10% glucose and saline + 10 c.cs.10% calcium gluconate
aet 10 mths.	½ hr.	8.58	Intra-venously
	1 hr.	9.12	
	2 hrs.	9.01	(Chronic Diarrhoea)
	3 hrs.	8.73	

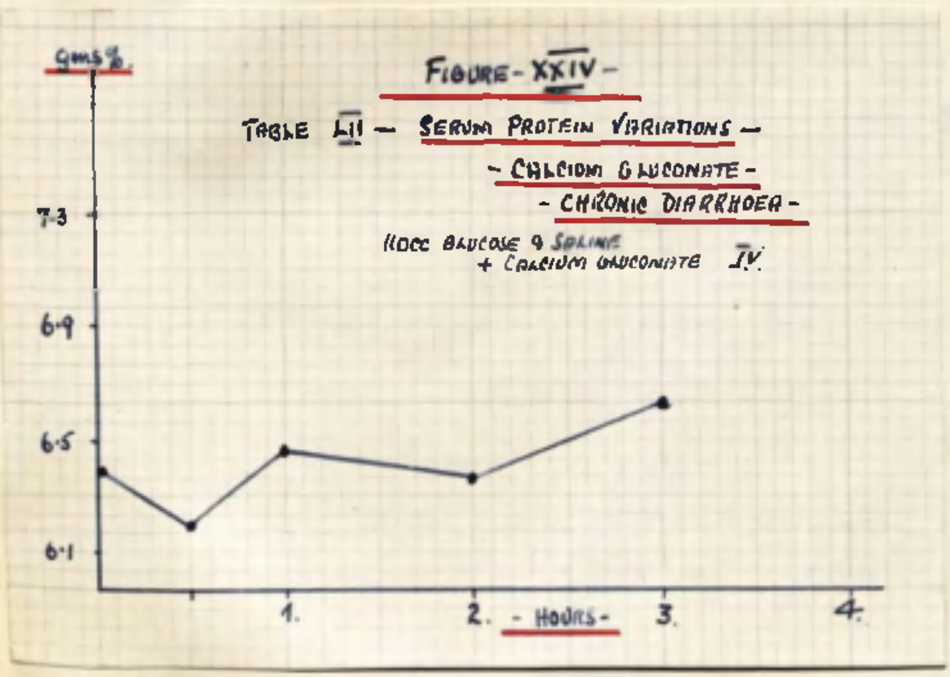


Four patients, two acute (Tables LIII and LIV), and two chronic (Tables LI and LII, Figs. XXIII and XXIV), suffering from infantile diarrhoea were given calcium gluconate along with glucose and saline injections and the resulting serum proteins studied. Clinically the addition of calcium gluconate to the injections did not appear to have any immediate effect on the patients' general condition. In only one patient suffering from chronic infantile diarrhoea was 10% calcium gluconate used, the others receiving the same quantity of calcium given in 20% solution. In both chronic cases the initial protein fall was minimal after injection, rose at one hour to a value higher than the pre-injection

TABLE LII.

Serum Protein after Calcium Gluconate - Diarrhoea.

Name	Time	Serum Protein gms.%	Remarks
(B.M.)	Before	6.38	110 c.cs.10% glucose & saline + 10 c.cs.20% calcium gluconate
aet 14 wks.	½ hr.	6.20	Intra-venously
	1 hr.	6.47	
	2 hrs.	6.36	(Chronic diarrhoea)
	3 hrs.	6.63	



level, and then fell gradually so that, in C.B., three hours after injection, the reading was still greater than in the first specimen removed. In the case of B.M., however, the serum protein value fell to the level of the pre-injection specimen, but at 3 hours again showed a marked rise.

TABLE LIII.

Serum Protein after Calcium Gluconate - Diarrhoea.

Name	Time	Serum Protein gms.%	Remarks
(B.I.)	Before	8.82	160 c.cs.10% glucose & saline + 10 c.cs.20% calcium gluconate
aet 11 months	½ hr.	7.72	Intra-venously
	1 hr.	8.91	
	2 hrs.	9.42	(Acute Infantile Diarrhoea)
	3 hrs.	9.34	

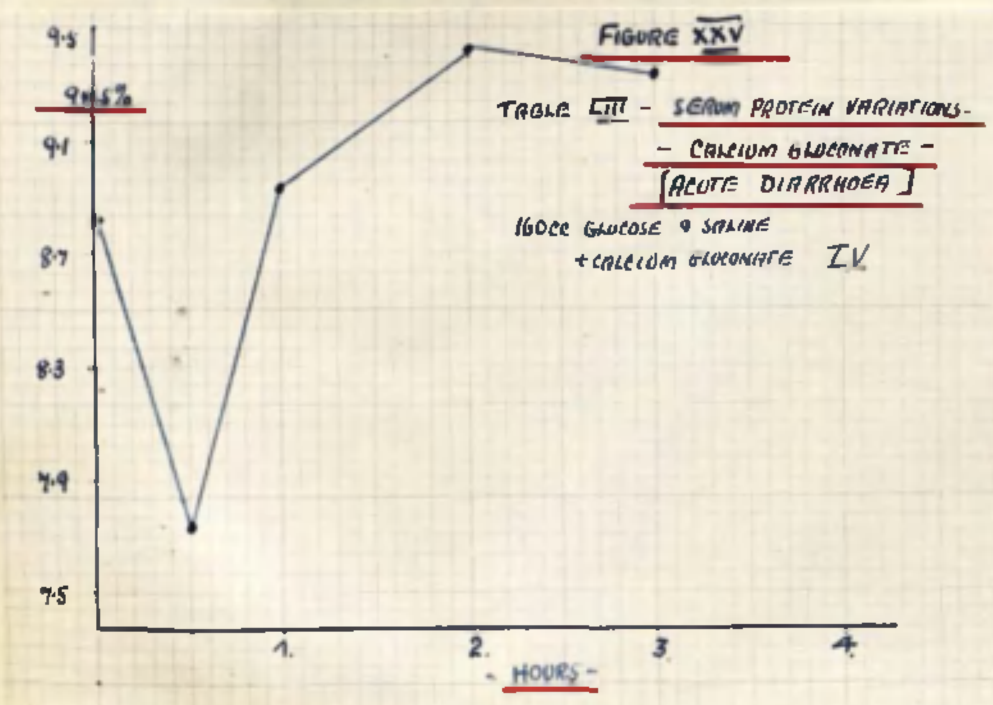


FIGURE XXV

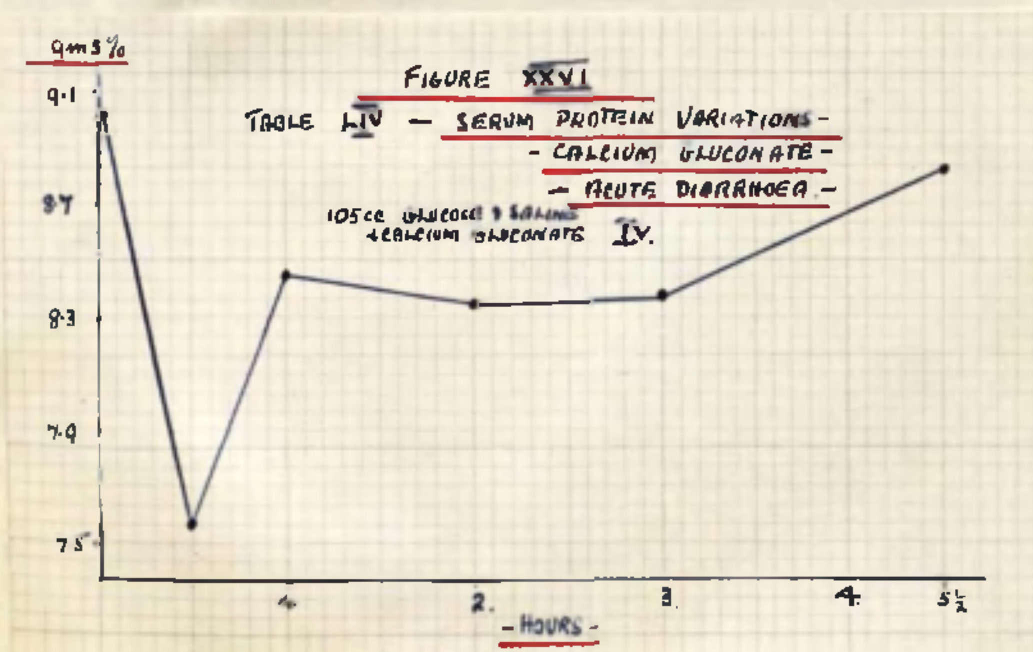
TABLE LIII - SERUM PROTEIN VARIATIONS - CALCIUM GLUCONATE - [ACUTE DIARRHOEA]

In the case of B.I., suffering from acute infantile diarrhoea, a large and significant fall of serum protein occurred as the result of the fluid injection, followed by a steady rise until at 2 hours it reached a value greatly in excess of the protein in the pre-injection specimen. At 3 hours the protein value showed a slight fall but still remained at a reading greater than the initial value of 8.82 gms.%.

TABLE LIV.

Serum Protein after Calcium Gluconate - Diarrhoea.

Name	Time	Serum Protein gms.%	Remarks
(M.B.)	Before	9.03	105 c.cs.10% glucose & saline + 10 c.cs.20% calcium gluconate
aet 16 wks.	½ hr.	7.57	
	1 hr.	8.46	
	2 hrs.	8.35	(Acute Infantile Diarrhoea)
	3 hrs.	8.37	
	5½ hrs.	8.84	



On the other hand M.B. (Table LIV; Fig. XXVI) showed, after the initial serum protein fall as the result of the injection, a more or less continuous rise for $5\frac{1}{2}$ hours at which time the serum protein reading was still lower than was found for the pre-injection specimen.

It would thus appear that in infantile diarrhoea, when calcium gluconate has been given, the serum proteins exhibit alterations peculiar to the individual patient. The employment of this substance however, appears to cause an increased movement of fluid from the circulation - serum protein taken as indicator. During such a short period as three hours, it is most likely that such movements of fluid could only be from the circulation into the tissue spaces.

(E). Post-Mortem Blood Values.

Interest was aroused in the post-mortem values of the blood constituents owing to the fact that in many cases of infantile diarrhoea the opportunity presented itself for the estimation of the chloride and water content of the tissues. It was considered important to discover whether any relationship existed between these tissues and the post-mortem blood values, with particular reference to chloride and water content.

In an examination of the literature very few examinations of the post-mortem blood appear to have been carried out, but Jacoby[82] demonstrated that in cadaver blood the non-protein nitrogen was about 70% higher than in normal individuals and became even higher after the lapse of another six hours.

The post-mortem blood samples in the series were usually removed within half an hour of death by means of a needle and syringe, which was passed through the chest wall and into the ventricle of the heart. One specimen thus collected was oxalated, the other left non-oxalated, and the constituents examined by the same methods as were used for ordinary blood samples.

(a) Non-diarrhoeal Infants.

TABLE LV.

Post-Mortem Blood Constituents.

Name	Time	Serum Protein gms.%	Blood N.P.N. mgs.%	Blood Chloride ccs.N/10 Cl	Blood Haematocrit	Disease
(M.M.) aet 1½ yrs.	15 min.	6.96	47.1	82.0	R.B.C.) 21.2% Plas.) 78.8%	(Broncho Pneumonia)

TABLE LVI

Post-Mortem Blood Constituents.

Name	Time	Serum Protein gms.%	Blood N.P.N. mgs.%	Blood Chloride ccs.N/10 Cl	Blood Haematocrit	Disease
(P.N.) aet 18 wks	20 min.	7.13	81.9	118.3	R.B.C.) 32.6% Plas.) 67.4%	(Pyelo nephritis)

In two infants, (Tables LV and LVI) dying from acute broncho-pneumonia and pyelo-nephritis respectively, the post-mortem blood values are tabulated. Both cases showed increased values for the non-protein nitrogen, while the blood chloride values were within normal limits in one and exceptionally high in the other. It should be noted however that the latter patient received several intra-venous and intra-peritoneal injections just before death, the effect of which would be to raise the blood chloride level, particularly if the renal function happened to be poor. The serum protein values were within normal limits in both patients while the plasma volume % (haematocrit) appeared normal in one case and high in the other.

(b) Infantile Diarrhoea Patients. The post-mortem blood values are tabulated for infants dying as the result of diarrhoea and are contrasted with the ante-mortem observations where these are available.

TABLE LVII.

Post-Mortem Blood - Diarrhoea.

Name	Time	Serum Protein gms.%	Blood N.P.N. mgs.%	Blood Chloride ccs.N/10 Cl	Remarks	Date
(F.C.) aet 12 wks.	Before	7.85	57.5	-	Five I.V. & one I.P. injections during last week.	21/4/35
	P.M.	-	-	110.1		28/4/35

TABLE LVIII.

Post-Mortem Blood - Diarrhoea.

Name	Time	Serum Protein gms.%	Blood N.P.N. mgs.%	Chloride ccs.N/10 Cl	Haematocrit	Remarks	Date
(A.S.) aet 24 wks.	Before	9.25	104.2	99.5	R.B.C.) 33.0% Plas.) 67.0%	Two I.V. injections	12/5/35
	P.M.	7.53	95.6	99.6	R.B.C.) 20% Plas.) 80%		13/5/35

The serum proteins showed very variable readings, being normal in some cases (Tables LVIII and LX), high in others (Tables LIX and LXI), and very low in one case (Table LXII).

TABLE LIX.

Post-Mortem Blood - Diarrhoea.

Name	Time	Serum Protein gms.%	Blood N.P.N. mgs.%	Chloride ccs.N/10 Cl	Haematocrit	Remarks	Date
(M.G.) aet 30 wks.	Before	6.31	17.9	70.35	-	One I.V. & two I.P. injections	6/6/35
	P.M.	12.02	72.4	71.6	R.B.C.)51.3% Plas.)48.7%	(None in last 7 days)	13/6/35

The non-protein nitrogen readings in all cases were very high, although it should be noted that in cases A.S. and B.O'H. (Tables LVIII and LXII) the values for this substance just previous to death were even higher than for the post-mortem blood.

The blood chlorides in many cases (Tables, LVII, LVIII, LX and LXII) also showed remarkably high readings, but in two (Tables LIX and LXI) the values were found to be within normal limits. In assessing the importance of these findings it should be noted that all the high chloride group received saline either by the intra-venous or intra-peritoneal route within a day or two of death.

TABLE LX.

Post-Mortem Blood - Diarrhoea.

Name	Time	Serum Protein gms.%	Blood N.P.N. mgs.%	Blood Chloride ccs.N/10 Cl	Remarks	Date
(I.S.) aet 40 wks.	Before	9.48	-	-	One I.P. injection just before death	21/8/35
	P.M.	7.85	71.4	125.3		21/8/35

The haematocrit values are not characteristic, the plasma volume % being high in one case (A.S., Table LVIII) and very low in another (M.C., Table LIX). In this latter case marked blood concentration appears to be present, confirmatory evidence being found in the serum protein reading - 12.02 gms.%.

TABLE LXI.

Post-Mortem Blood - Diarrhoea.

Name	Time	Serum Protein gms.%	Blood N.P.N. mgs.%	Blood Chloride ccs.N/10 Cl	Remarks	Date
(H.McN.) aet 32 wks.	Before	9.93	97.4	84.7	Two & three I.P. & I.V. injections	4/9/35
	P.M.	9.44	125.0	86.16	(None in last 3 days)	10/9/35

TABLE LXII.

Post-Mortem Blood - Diarrhoea.

Name	Time	Serum Protein gms.%	Blood N.P.N. mgs.%	Blood Chloride ccs.N/10 Cl	Remarks	Date
(B.O'H.) aet 20 wks.	Before	6.59	147	105.1	Nine I.V.& I.P. injections.	13/9/35
	P.M.	4.06	125	116.4		14/9/35

The findings for the blood constituents in these infants, dying as the result of infantile diarrhoea, appear to be somewhat similar to the findings in patients dying from non-diarrhoeal causes, except that there seems to be a more marked tendency to blood concentration and also a greater increase in the blood chloride. It must be remembered however that many cases with very high blood chloride values had received saline shortly before death.

(F). Relationship between Blood Chloride and Tissue Chloride.

When the average tissue chloride values and the post-mortem blood chloride figures are compared (Table LXIII), it looks as if there was a close relationship between them. In only one case (M.C.) was the post-mortem blood chloride value within normal limits, and in this infant alone the tissue chloride values appear low as compared with the tissue chloride values of other patients. It should also be mentioned however that in this case no saline was administered during the last week of life, while to all the other patients of this series varying amounts of saline and glucose were given within a week, and in some instances, within a few days of death.

TABLE LXIII

Post-Mortem Blood and Tissue Chlorides.

(Chloride expressed in c.cs.N/10 Cl.)

Name	Age wks.	Liver	Lung	Kidney	Muscle	Heart	Brain	P.M. Blood	Disease
(P.N.)	18	43.5	82.7	63.7	65.5	50.0	65.6	118.3	Pyelo Nephritis
(F.C.)	12	47.7	74.6	53.9	60.0	54.8	56.3	110.1	D. & V.
(B.O'H.)	20	72.2	-	73.3	51.4	68.3	47.7	116.4	D. & V.
(M.C.)	30	27.5	51.0	40.0	45.0	36.0	59.3	71.6	D. & V.
(I.S.)	40	60.0	71.8	50.5	77.1	56.1	-	125.2	D. & V.
(A.S.)	24	48.4	72.1	60.0	50.8	61.7	-	99.5	D. & V.

D. & V. = Diarrhoea and vomiting.

It thus appears that the administration of saline and glucose has some effect in raising both the tissue and the blood chloride values.

Discussion.

The effect of repeated saline and glucose injections on the blood constituents of patients suffering from acute infantile diarrhoea is a definite lowering of the serum protein and, in some cases, the non-protein nitrogen. No doubt the amount of fluid administered plays an important part in this fall, for adequate volume appears essential to institute a satisfactory renal action, without which the N.P.N. value will not diminish. In the case (J.M., Table XXVI) in which there first occurs a fall, in both the serum protein and N.P.N., but later a rise in these substances, it may be suggested that insufficient fluid had been administered to rehydrate the tissues and institute a satisfactory renal response. In several of the other patients, where blood specimens were removed shortly before death, a marked increase in the N.P.N. value is noted, which appears to be due not only to an increased tissue protein destruction but also to a diminished excretory action of the kidney, apparently a natural phenomenon in moribund patients[82].

In several of these patients, where the symptoms were very acute and the child toxic, acidotic and very dehydrated, the effect of saline and glucose injections was an increase in the blood chloride value. This increase of the chloride was also noted by Hartmann[21] and led him to lay stress on the danger of an increase of chloride at the expense of bicarbonate, resulting in the production of a chloride acidosis. For this reason he and others[22],[41] have been adamant in affirming the importance of avoiding isotonic saline in the treatment of these infants. As no determinations on the bicarbonate value of the blood were carried out in any of the present series, these views cannot be confirmed, but it may be suggested that the chloride retention is due either to lack of water, necessary for the excretion of chloride, or to the fact that these cases were in extremities and kidney function was at a minimum. The former view appears more likely. Nonnenbruch[83] has stated that when water intake is poor - as occurs in diarrhoea - chloride may be retained without water. It is thus suggested that provided sufficient fluid, preferably glucose and saline, by perhaps the continuous intra-venous drip method (see later) is administered, chloride retention in the blood will not take place since any excess chloride will be removed, along with the products of metabolic break-down, by the induced kidney action of this large volume of fluid.

The serum protein variations, occurring over a period of one to five hours after fluid injections in normal infants, appear to be similar to those described by Miller et alii[43](76) in animals. From a careful examination of the existing literature this series appears to be the first described in infants.

During such a short space of time, the rapid and marked alteration of serum protein can only be due to alteration in the plasma volume.

It would appear that, as the result of saline injections, there immediately occurs an increase of the plasma volume which gradually recedes until at one hour, in most cases, it is smaller than the volume previous to the saline administration (Tables XXVII, XXVIII, XXIX and XXX). This diminution in volume can only be explained by the fact that, immediately after the injection, the additional fluid is removed from the circulation. Most of it must pass to the tissue spaces and the water depots of the body, as the kidneys would find it impossible to deal with such a quantity of fluid within the short space of one hour. In several patients, (Tables XXVII, XXIX and XXX), it was noted that, at one hour, more fluid left the circulation than was administered - indicated by the higher serum protein value at this period than before the injection was given. It is thus evident that the circulation, in an attempt to remove the excess fluid, oversteps the mark and loses not only the introduced fluid but also fluid previously in the blood stream. At two hours however, due to passage of fluid back from the tissues to the circulation, the serum protein shows a fall as compared with the value at one hour, but at three hours the plasma volume returns to the vicinity of its pre-injection value.

These findings indicate that, as the result of fluid injections in normal infants, a to-and-fro movement of fluid takes place between the blood plasma and the water depots of the body until, after the lapse of 3-4 hours, the normal water content of the plasma and tissues is reached. This is probably due to action of the kidneys, expelling the injected fluid. In one normal case (Table XXVIII) the movements of fluid from the circulation to the tissues were not well marked although a definite return to the circulation did occur - serum proteins fell from 5.96 to 5.40 gms. % between one and two hours. This inconsistency cannot be satisfactorily explained, for this patient, although suffering from hydrocephalus, showed no evidence of any upset during the three hours following saline injection.

The mechanism regulating the passage of fluid from one tissue to another is not definitely understood, but the fact that several authors (77),(78) have shown that, in dogs with a lowered blood pressure, fluid passed very much more slowly from the circulation into the tissue spaces than in dogs with a normal blood pressure, would seem to indicate the importance of blood pressure as a regulating factor. There is also no doubt, that osmotic action and the affinity of the water depots and tissue spaces of the body for fluid, take a part in these movements.

In patients suffering from acute infantile diarrhoea there also occurs a definite increase in the plasma volume as the result of saline and glucose injections - shown by the fall of serum protein at period ½ hour after injection - but the plasma remains diluted for longer periods than occurs in normal infants. The maximum concentration of serum protein in many of these patients did not occur until 2 hours after the injection (Tables XXXIV, XXXV, XXXVII and XXVIII). At this period the concentration of the plasma never exceeds the pre-injection value; a common finding however in the case of normal infants. In the acute diarrhoeal infant in which serum protein variations are similar to normal, the maximum concentration of plasma volume, as reflected by the serum protein reading, occurs one hour after the injection (Table XXXVI). It is however evident that the amount of fluid passed either into the tissues during the first hour, or back into the circulation during the second hour, is never as great as in normal patients. The slower and smaller fluid alternations between the circulation and the tissues in cases of acute infantile diarrhoea must be due to:

(a) a lowered blood pressure[77],[78]

or (b) Increased affinity of the circulation for fluid[75]

or (c) Diminished affinity of the tissues for fluid

or (d) Some other abnormality such as alteration of osmotic pressure. An increased concentration of the blood constituents has been shown to occur in most cases of acute infantile diarrhoea. This finding might easily explain the apparent increased affinity of the circulation for the injected fluid. If Gambles'[69] suggestion, that the blood acts only as a vehicle for the transport of water (from the fluid depots to the site of fluid-need, in this case, the bowel) be correct, then it appears quite natural that the movements of injected fluid between the circulation and the tissues will be cut down to a minimum. The conveyance of fluid to the acutely inflamed bowel will be of paramount importance, the fluid depots receiving only the excess not required there.

The possibility that low blood pressure also plays an important part in this diminished movement of fluid must be considered. The fact that the tissues are necessarily involved in any alteration of metabolism led to the estimation of their water content. This is dealt with in a later section (Part IV), but it may be stated here that from examination of the results no definite diminution of the water content of the tissues, with the exception of liver, was found in acute infantile diarrhoea.

No definite cause can be determined for this slow and diminished movement of injected fluid, in cases with acute infantile diarrhoea, but probably the marked blood concentration and, to a less extent, a lowering of the blood pressure play the most important parts in its production.

In several infants suffering from chronic infantile diarrhoea, the alterations of plasma volume, reflected by the serum protein variations, indicated (Tables XL, XLII and XLVI) activities resembling those found in normal infants, except that a smaller amount of fluid passes to and from the tissues. One infant (Table XLI) showed variations similar to those of the acute patients, but the remainder did not exhibit any particular or characteristic alterations. It would thus appear that, in some of these patients with chronic diarrhoea, the normal movements of fluid between the circulation and the tissues is also upset but to a much less marked extent than occurs in the acute cases. In others, however, the movements appear even more exaggerated than those found in normal infants.

The effect of saline and glucose injections with calcium gluconate, in normal infants, caused a diminution in the fluctuations of fluid between the tissues and the blood plasma, due no doubt to the action of calcium in diminishing the permeability of capillaries.

In cases suffering from infantile diarrhoea, the serum proteins exhibited marked variations as compared with similar cases not receiving calcium gluconate. In three of the four patients examined (Tables LI, LII and LIII) the plasma volume, as reflected by the concentration of serum protein, at one hour indicated a marked decrease, which was maintained at two hours in two patients (Tables LI and LIII), and was present in all three at the end of three hours.

These results would indicate that the action of calcium gluconate resulted in a more rapid transfer of the injected fluid from the circulation most probably to the tissue spaces.

It is tentatively suggested that calcium gluconate should be used, when administering saline and glucose injections to these infants suffering from diarrhoea and vomiting, as it tends to force the injected fluid from the circulation at a more rapid rate. It is possible that more fluid could be administered, when this substance is used, without causing embarrassment of the circulation since the injected fluid is passed more rapidly into the tissues.

Post-Mortem Blood Values.

The post-mortem blood values, in infants dying from conditions other than dehydration or the effects of infantile diarrhoea, show variable results but in all cases the non-protein nitrogen was raised well above the normal level. In one case (Table LVI), suffering and dying from pyelo-nephritis, to whom saline was administered within a few days of death, the blood chloride was very high, no doubt because of kidney dysfunction just before the fatal termination.

In all the patients dying from infantile diarrhoea and dehydration the non-protein nitrogen values were high while the chloride was also high, especially in those cases receiving saline just before death. This suggests that, as the result of kidney dysfunction and tissue protein breakdown commencing shortly before death, there occurs a marked accumulation of non-protein nitrogen and chloride.

Some relationship appears to exist between the chloride value of the post-mortem blood and the chloride value of the tissues for, in all cases in which a high post-mortem blood chloride was found, similar findings were noted in tissues from the same patient. In one patient, who received no saline for the seven days preceding death, both the post-mortem blood chloride and the tissue chloride values were within normal limits.

Summary.

The serum protein values in a group of normal infants are studied. There is no apparent relationship between the serum protein value and the age.

The serum proteins and non-protein nitrogen values, in most cases with acute infantile diarrhoea and vomiting, are high but the plasma volumes % (Haematocrit) and the blood chlorides show variable readings.

The administration of saline generally causes an increase of the blood chloride in acute and toxic infants. The significance of this finding is fully discussed and it is concluded that it is due to loss of water without accompanying chloride excretion.

As a result of saline and glucose injections characteristic alterations occur in the serum proteins of normal infants.

There appears to be some abnormality of plasma volume variations (indicated by serum protein) in both acute and chronic infantile diarrhoea after saline and glucose injections.

The effect on the plasma volume of saline and glucose with the addition of calcium gluconate has been studied in normal infants and results in a diminution of fluid movements between the circulation and the tissues.

In infantile diarrhoea it may tentatively be suggested that calcium gluconate seems of some benefit in accelerating the movement of fluid from the circulation to the tissue spaces.

The post-mortem blood values are given for cases with and without diarrhoea and a direct relationship between the post-mortem blood chloride and the tissue chloride values is shown.

PART III.

Experimental Studies on the Blood and Tissues of Rabbits after the Injection of Intra-peritoneal Solutions of Hypotonic Saline and Glucose.

PART III.

Experimental Studies on the Blood and Tissues of Rabbits after the injection of Intra-Peritoneal Solutions of Hypotonic Saline and Glucose.

Darrow and Yannet[84] have shown that in the case of dogs, rabbits and monkeys, changes occur in the distribution of body water as the result of an increase or decrease in the extra cellular electrolyte. They found that all the stages, from mild to severe dehydration, could be produced in these animals by the use of intra-peritoneal injections of hypotonic solutions of 5% glucose. The tongue and mucous membranes became dry, the skin lost its turgor, and, in rabbits, a greyish pallor such as is seen in cases of "alimentary toxaemia" was observed. The animals usually recovered after the lapse of 24 hours. They were also able to demonstrate in those animals alterations in the serum protein, blood chloride and haematocrit readings for the duration of the experiments.

The object of this section of the paper was if possible to confirm the findings as set down by the above authors[84] and by estimating the chloride and water content of animal tissues, to correlate these if possible with the alterations in the blood constituents. It is at once obvious that any change in distribution of body water, the result of extra-cellular electrolyte alteration, would be of the greatest importance in relation to dehydration and its treatment, as met with in cases suffering from infantile diarrhoea and vomiting.

Methods.

The animals used in these experiments were normal rabbits taken from stock. The various injection fluids were prepared in the Bio-Chemical Laboratory, while all the experimental procedures were carried out in the Pathological Department. In all animals 100 c.c. of fluid per kilogram of body weight was administered by the intra-peritoneal route. Sufficient quantities of both oxalated and non-oxalated blood were removed from the ear of these animals, for estimation of blood and plasma chloride, plasma and R.B.C volume (haematocrit), serum protein (Zeiss refractometer), blood sugar (Folin Wu), serum fat and blood cholesterol. The blood specimens were removed (a) just before the injection and (b) four to five hours later.

The procedure adopted for intra-peritoneal injection was that a small area of the abdominal wall was shaved and the previously measured quantity of fluid slowly allowed to pass in by means of a funnel, tubing, and a fine needle. After the lapse of 4-5 hours the animals were killed and all the fluid remaining in the peritoneal cavity was carefully collected by means of a pipette and measured. A definite small quantity which could not be recovered by this means was collected and its volume estimated by the use of previously weighed dry swabs. In this manner the total fluid volume in the peritoneal cavity was accurately measured. During the course of the experiment no food or drink was allowed them and although the amount of urine was not measured, this amounted to only small quantities in some cases and none in others. Various tissues were also removed and analysed immediately for their chloride and water content, the methods employed in this procedure being exactly similar to these in the case of infant tissues (44).

(A). Blood alterations after the Intra-peritoneal injection of 0.2% NaCl.

The serum proteins, serum fat, blood cholesterol, blood sugar, non-protein nitrogen, blood and plasma chloride, and the haematocrit in a series of three rabbits (Table LXIV) were examined, the specimens being removed (a) before and (b) 4-5 hours after the intra-peritoneal injection of 0.2% NaCl.

The animals were closely observed after these injections but none of them appeared in the least affected by the injection of fluid nor were any signs of dehydration present.

TABLE LXIV.

Rabbit C.I. Wt.1.0 Kg. Injection 100 ccs. 0.2% NaCl 10 a.m.: Killed 2.45 p.m.
C.II. " 2.04 " " 204 " " 11 " " 3.30 "
C.III. " 2.06 " " 206 " " 10.30 " " 3.15 "

	Serum gms. %		Blood mgs. %			Blood Chloride	Plasma Chloride	Haematocrit %		Resid. Fluid
	Protein	Fat	Chol.	Sugar	N.P.N.	ccs.N/10 Cl.		R.B.C.	Plasma	ccs.
C.I (a)	6.85	0.18	124.1	96.2	56.1	80.0	97.3	37.1	62.9	
(b)	5.27	0.12	108.4	124.2	27.7	82.2	103.1	32.5	67.5	11.2
C.II (a)	6.20	0.16	117.2	89.2	29.2	87.9	108.9	39.0	61.0	
(b)	5.13	0.16	114.3	123.4	28.7	84.4	103.1	33.7	66.3	Nil
C.III (a)	6.88	0.20	108.4	57.4	27.5	76.2	105.4	41.3	58.7	
(b)	4.94	0.16	111.5	142.8	33.3	77.4	95.0	35.2	64.8	58

From the tabulated results it will be noted that the serum proteins show reasonably constant values in the first specimen (a) of all three animals, the variations amounting to only 0.6 gms. %. Similarly the serum fat, the blood and plasma chloride, the R.B.C. and plasma volume % exhibit readings closely related and well within normal limits. Slight variations in the blood sugar and the non-protein nitrogen values are however observed but for practical purposes these may be considered to be normal.

On exposure of the peritoneal cavity after the death of the animal and four to five hours after the injection, no free fluid was found in CII, only 11.2 c.c. in CI, and the largest amount - 58.0 c.c. - in CIII (Table LXIV). It would thus appear that a rapid removal of 0.2% sodium chloride from the peritoneal cavity occurs in all these animals.

A marked fall in the serum protein values of all three cases is at once noticed on examination of the second blood specimen (b). This fall was most marked in the case of CIII. These findings would thus indicate that during the period between the removal of the two blood specimens an increase of plasma volume occurred, due most probably to the passage of the injected intra-peritoneal fluid into the circulation. This supposition is further strengthened by the fact that in all cases a definite and significant increase of plasma volume % also occurred. The blood chloride, serum fat and cholesterol values show only slight alterations but, in the case of rabbit CI, a marked fall in the non-protein nitrogen occurred. A definite increase of blood sugar occurred in all three animals, which was not expected and cannot be satisfactorily explained.

In the case of rabbit CI the fluid recovered from the peritoneal cavity was found to contain a moderate amount of protein (not calculated). The presence of this protein no doubt accounts to some extent for the lowering of the serum proteins, but is not sufficient to account for the marked fall observed, as the total amount present in 11.2 c.c. of fluid would not have any appreciable effect on the total protein in the circulation.

(B). Blood alterations after Intra-peritoneal injection of 5% glucose.

The blood constituents were examined in a similar series of three rabbits in which 5% glucose was introduced into the peritoneal cavity, the same time factors and proportionate amounts of fluid being used as in the previous series.

As a result of these intra-peritoneal injections no definite alteration in the general condition of the animals was observed, nor did any signs of dehydration or "toxaemia" occur, but it was nevertheless noticed that they appeared to be less active than those of the first series. Great difficulty was experienced in this series of animals, in collecting samples of blood four to five hours after the injection, owing to increased coagulability.

TABLE LXV.

Rabbit C.IV. Wt.2.36 Kg. Injection 236 c.c.5% Glucose 10.10 a.m.: killed 3.30 p.m.
C.V. " 2.20 " " 220 " " 11 " " 4.0 "
C.VI " 2.13 " " 213 " " 10.20 " " 3.30 "

	Serum gms.%		Blood mgs.%			Blood ccs. $\frac{N}{10}$ Cl.	Plasma	Haematocrit %	
	Protein	Fat	Chol.	Sugar	N.P.N.	Chloride	Chloride	R.B.C.	Plasma
C.IV (a)	6.16	0.20	124.1	75.1	28.4	73.8	98.0	32.2	67.8
(b)	8.78	0.24	127.6	1740.0	21.7	61.7	73.8	39.0	61.0
C.V. (a)	6.44	0.20	124.1	73.5	26.3	85.9	98.0	25.0	75.0
(b)	7.48	0.24	120.7	689.6	23.5	72.7	95.8	37.8	62.2
C.VI (a)	5.34	0.20	131.0	80.6	33.3	79.3	94.7	36.5	63.5
(b)	7.68	0.24	140.9	2105.0	25.7	59.6	74.5	Specimen lost	

TABLE LXV (a).

	Pleural Exudate			Peritoneal Fluid				Sugar Content of Injection gms.%
	Amount c.c.	Chloride cc $\frac{N}{10}$ Cl	Sugar gms.%	Amount c.c.	Protein	Chloride cc $\frac{N}{10}$ Cl	Sugar gms.%	
C.IV	17.5	77.1	1.734	353.9	+++	61.7	2.22	5.156
C.V	9.75	85.9	0.656	235.6	+++	77.1	2.941	5.156
C.VI	10.5	77.1	1.904	193.8	+++	73.8	2.126	5.263

Examination of the blood constituents in the specimen (a), removed before injection, shows variations in the plasma and R.B.C. volume %, but the other figures are normal.

The blood constituents in the case of the second specimen (b) taken just before the death of the animals and four to five hours after the first (a) exhibit however large and surprising alterations. In all three animals (Table LXV) a definite increase in the serum protein values resulted, while a diminution of the plasma volume % in two of the animals (CIV and CV) was noted. The plasma and R.B.C. volume % in the case of CVI are not tabulated owing to the loss of one specimen, but in this case a marked increase in the serum protein value also occurred. Therefore it may be accepted that in all these animals a marked diminution of the plasma volume occurs, due no doubt to water shift. The blood sugar exhibits a marked rise, the blood and plasma chloride a marked fall, the N.P.N. a small fall, while the cholesterol and fat show no very significant alterations except a slight increase of fat in all three animals.

On killing the animals and opening the peritoneal cavity it was found that the volume of fluid recovered was greater than the amount injected in rabbits CIV and CV, and only slightly less than this amount in CVI. Similar findings have been noted by Schechter et alii [86] in the case of dogs to which 5% intraperitoneal glucose had been administered.

No evidence of inflammation or hyperaemia of the alimentary vessels was noticed in any of these rabbits when the perito-

:neal cavity was opened. On analysis of the fluid recovered from the peritoneal cavity a comparatively large amount of protein was present in all specimens, while the peritoneal sugar content had fallen to nearly half its original value. The peritoneal chloride readings were closely related to but lower than those of the blood plasma (specimen (b)). As no fluid was lost from the body during the experiment, these alterations of the blood and the intra-peritoneal fluid can only be explained by the fact that what the blood loses the intra-peritoneal fluid gains, and vice versa.

On exposing the lungs in these animals a small amount of blood stained or clear fluid was recovered from the pleural cavity. This fluid showed the presence of protein, sugar and chloride, the latter two constituents exhibiting values similar to the blood (specimen (b)). The presence of fluid in the pleural cavity was not anticipated and cannot be satisfactorily explained although it may possibly be due to the effect of sudden changes in blood concentration on the delicate capillaries on the lung and pleural surface.

(C). <u>Chloride and Water content - Various tissues.</u>

The lung, liver, heart, brain, muscle and kidney tissues of these animals were also examined to discover whether any alterations similar to those of the circulation occurred as the result of intra-peritoneal injection of 0.2% and 5% glucose respectively.

TABLE LXVI.

Chloride and Water Content - Various Tissues.

Rabbit	Fluid given	Liver		Lung		Kidney		Muscle		Heart		Brain	
		Chlor. ccs. N/10	H_2O %	Chlor. ccs. N/10	H_2O %	Chlor. ccs. N/10	H_2O %	Chlor. ccs. N/10	H_2O %	Chlor. ccs. N/10	H_2O %	Chlor. ccs. N/10	H_2O %
C.I.	0.2% NaCl	28.2	75.0	54.0	73.7	62.1	79.3	8.7	78.4	30.1	80.2	28.0	77.2
C.II	"	28.5	73.5	45.9	79.0	45.7	79.0	7.7	77.1	17.3	81.1	28.5	77.2
C.III	"	26.3	75.1	55.8	79.3	50.1	77.3	8.7	76.7	28.0	80.0	30.0	78.2
Average		27.6	74.5	51.9	77.3	52.6	78.5	8.3	77.4	25.1	80.4	28.8	77.5
C.IV	5% Glucose	18.9	74.3	44.4	77.0	31.2	76.0	8.6	74.8	25.3	73.6	35.8	78.3
C.V	"	21.8	77.0	46.0	80.0	36.0	81.3	10.8	78.2	34.1	80.1	28.4	77.2
C.VI	"	13.1	73.3	41.2	79.0	23.7	76.8	6.3	73.7	22.3	75.7	27.3	79.2
Average		17.9	74.8	43.8	78.6	31.9	78.1	8.6	75.6	27.2	76.5	30.5	78.2
* Normal		22.7± 5.20	71.8± 0.9	51.0 ± 9.14	79 ± 1.00	39.9± 12.96	76.4± 1.0	11.2± 2.74	76.2 ± 1.8	29.9± 4.15	80.6 ± 0.6	30.6± 5.09	77.6± 0.2

* Blacklock and Morris[85].

On a close examination of these results (Table LXVI) no apparent alteration of the water content of the various tissues occurs. The chloride content of the liver, lung and kidney appear diminished however in the second series of animals (CIV, V and VI) while the content for muscle, heart and brain exhibits a rather close relationship throughout both series. It is problematical whether this loss of chloride in liver, lung and kidney is due to the action of the intra-peritoneal glucose solution. It must be remembered that two of these tissues - liver and kidney - come into rather close relationship with the intra-peritoneal fluid and may be affected by such contact. Also lung, liver and kidney, contain comparatively large amounts of blood and any alteration in the chloride content of this will reveal itself more markedly in these tissues than in heart, muscle or brain. The fact that no definite alteration occurs in the chloride content of the latter, or in the water content of any tissue, rather suggests that this deficiency, i.e. low lung, liver and kidney chloride, is not characteristic of a general tissue chloride loss.

Discussion.

These results demonstrate rather conclusively that the action of 0.2% NaCl and 5% glucose solutions respectively, when introduced into the peritoneal cavity of rabbits, leads to marked and opposite alterations in the circulating blood. This is rather interesting as in both series of animals the fluid administered was a hypotonic solution. These alterations occurring in the blood as a result of injecting the two solutions must depend to a great extent on their different diffusion rates.

In the case of the first, 0.2% NaCl, fluid immediately diffuses from the peritoneal cavity into the circulating blood stream owing to the greater osmotic action of the latter, while chloride and electrolyte pass from the blood into the peritoneal cavity. In this passage of electrolyte to the peritoneal cavity a certain quantity of water accompanies it, but the diffusion rate of fluid in the opposite direction is so much greater that after the period of 4-5 hours all the injected fluid is found to have left the peritoneal cavity. In the case of the glucose solution however, owing to its slower diffusion rate as compared with chloride, electrolytes accompanied by a certain amount of plasma fluid pass from the circulation into the peritoneal cavity and result in the large quantity of fluid present 4-5 hours after the injection in these animals. It is also probable that the action of glucose on the delicate cells of the peritoneal cavity, lead to some slight degree of irritation or damage, resulting also in a slowing of the absorption rate. The fact that some damage does occur is suggested by the presence of quite marked amounts of protein in the residual peritoneal fluids recovered after the death of the animals.

The extra amount of fluid present in the peritoneum of CIV and CV is however not sufficient to account for the marked lowering of the plasma volume found in the circulation. This marked diminution of plasma volume is probably due not only to the extra fluid present in the peritoneal cavity but also to fluid and plasma in the subcutaneous tissue spaces in close relationship to the peritoneum, through which diffusion and absorption must take place. Darrow and Yannet[84] have demonstrated that a fall in the cell protein occurs in their cases and suggest that this fall is due to an increase of water in the R.B.C.'s themselves owing to the loss of electrolytes from the plasma to the peritoneal cavity. The diminution of the blood and plasma chloride is very easily understood as the amount lost by the circulation can be calculated and is equivalent to that present in the peritoneal fluid.

As a result of the tissue chloride and percentage water determinations in these animals it would appear that only the circulation and possibly also the subcutaneous tissue spaces in relation to the peritoneum, play a part in these electrolyte and fluid alterations as the result of injecting intra-peritoneally hypotonic solutions of glucose.

Conclusions.

The results in the case of rabbits to which 5% glucose was administered intra-peritoneally confirm the findings of Darrow and Yannet[84].

The dangers of administering 5% solutions of glucose intra-peritoneally in dehydrated animals or infants should be appreciated.

The observation that 0.2% NaCl was rapidly absorbed from the peritoneal cavity and caused an increase of plasma volume appears of some importance and might be useful in treatment.

Summary.

The action of 0.2% NaCl injected intra-peritoneally in the case of rabbits, caused no marked ill effects; it was rapidly absorbed and led to an increased plasma volume % and a fall in serum proteins (i.e., a dilution of the plasma probably took place).

The action of 5% glucose resulted in a marked concentration of the circulating blood volume, and large quantities of fluid were present in the peritoneal cavity four to five hours after injection.

No significant alterations of chloride or water occurred in the fixed tissues of the body as the result of glucose injections.

PART IV.

Observations on Water and Chloride Content of Tissues with Variations due to Age, Duration of Illness, Temperature, etc.

PART IV.

Changes in Water and Chloride Content of the Tissues in Infantile Diarrhoea and Other Conditions.

Introduction.

Chloride plays a very important part in the general metabolism. It is involved in regulation of the water exchanges of the body and the neutrality of the tissue fluids, matters which are specially important in the early months of life. The chloride is replenished by food and is excreted mainly by the urine and sweat. Although normally only small amounts are lost by the bowel, in diarrhoea the faecal fluid may contain as much as 15 grams NaCl per litre[(34)]. Other pathological conditions such as diuresis, vomiting or profuse sweating, may reduce to a dangerous degree the chloride of the body and with it the water reserves of the organism. Under conditions such as these, excessive loss of chloride through one channel causes a diminished excretion in others; e.g. infants suffering from pyloric stenosis show a diminished output of urinary chloride owing to excessive loss by the vomitus.

We also know that water is an essential factor in the life of the organism. Its presence is essential in animal life for the bio-chemical changes which are constantly taking place, as a medium for cell nutrition and also as the vehicle for the transfer of waste products resulting from growth and metabolism.

It serves as the main agent in dissipation of the heat in fever, thereby assisting in regulation of temperature. According to Underhill and Fisk [87] the amount of water that can be mobilized for any one function probably depends on the quantity of available "free" or interstitial water present in the tissues. This "free" water is presumably liquid at ordinary temperatures, chemically uncombined and therefore capable of being shifted about via the blood stream. This is contrasted with the "bound" or intra cellular water which probably exists combined with salts and proteins and forms an integral part of the tissues themselves. Its loss would immediately lead to tissue death. From their experimental work on adults, Wiley and Wiley [55] believe that the "bound" water is drawn upon when the organism is in great need of fluid.

In all cases where large quantities of chloride are lost from the body there also occurs a corresponding loss of water, so that sooner or later signs of dehydration become evident. Water as well as chloride is essential, in the treatment of this type of case, before the tissues and body fluids can regain their normal content; not till then will tissue function and the excretion of waste products recommence.

It is obvious that, as the metabolic processes in the tissues are constantly in a state of flux, there cannot be a definite "normal" chloride or water content for any of them. Therefore, the average range of chloride and water concentration must be investigated by analysis of tissues from cases of sudden death, and suitable cases are rare in infancy.

A careful search of the literature revealed the paucity of such estimations in both adults and children but more particularly in the case of the latter. The average tissue chloride values for infants, quoted by several observers, are tabulated in Table LXVII. This includes a series of 6 infants, dying from various causes, reported by Morris and Graham[88], but these unfortunately cannot be considered as normal.

TABLE LXVII.

Tissue Chloride Values - Infants.

in c.cs. $\frac{N}{10}$ Cl.

Author	Kidney	Muscle	Heart	Lung	Liver	Brain
Morris & Graham[88]	42.1	43.2	37.7	52.4	36.5	48.9
Van Noorden[89]	Average for Body of Newly-born 52.9					

In adults Magnus-Levy[90] has estimated the values for the chloride in tissues obtained from a case of suicide, while Ballif and Gherscovice[91] got their figures from three cases of accidental death. Müller and Quincke[92] have also estimated the average chloride content of tissues obtained from 5 adult cases killed in accidents. The findings of these three authors may profitably be compared, in spite of the age difference, and are set down for this purpose in Table LXVIII. It will be noted

TABLE LXVIII.

Tissue Chloride Values - Adults - Accidental Deaths.

in c.cs. $\frac{N}{10}$ Cl.

Author	Kidney	Muscle	Heart	Lung	Liver	Brain
Magnus Levy (90)	59.3	17.4	34.7	63.5	42.3	36.8
Ballif & Gherscovici (91)	-	21.2	-	-	-	44.5
Müller & Quincke (92)	39.0	21.3	-	50.0	33.3	-

that Levy (90) demonstrated a rather high chloride content in kidney tissue. This has been confirmed by Blum and Broun (93) (Table LXIX) who found even higher values for this tissue in their series, and suggested that the kidney normally has the greatest average chloride content because it serves as the main agent in the excretion of chloride. These high values for kidney tissue are not confirmed by other investigators (92)(91) (Tables LXVIII and LXIX).

TABLE LXIX.

Tissue Chloride Values - Non-azotaemic Adults.

in c.cs $\frac{N}{10}$ Cl.

Author	Kidney	Muscle	Heart	Lung	Liver	Brain	Description
Baliff & Gherscovici (91)	26.8	- no figures quoted -				69.7	60 cases
Blum & Broun (93)	115.8	56.5	-	-	49.6	55.3	Non-azotaemic cases.
Rene S. Mach (62)	42.3	22.8	28.3	-	29.4	28.1	Pyloric stenosis

Ballif and Gherscovici[90], in a series of sixty adult patients dying from various causes, found great variations in the different tissues, some showing a chloropaenia others a chloropexia, but they mentioned that brain tissue appeared to be the tissue of election for fixation of chloride.

Various diseases apparently lead either to a retention or a loss of chloride from the tissues. Thus, von Moraczewski[94], Hutchison[95] et alii[96] have shown that in adult cases of pneumonia there is an increased retention of chloride, not in any one particular tissue but in the body tissues as a whole. In patients suffering from obstructive vomiting, due to pyloric stenosis or high intestinal obstruction, Brown, Eusterman et alii[97],[62],[100] have demonstrated a marked chloropaenia of most tissues. Morris and Graham[88] have similarly demonstrated a tissue chloropaenia in untreated pyloric stenosis, while the experimental work of Haden, Orr[98] et alii[99],[101],[102] has definitely proved that in animals with high intestinal obstruction a diminution of the chloride content of the blood and all the tissues of the body occurs. Thus great loss of chloride is due to the presence in the vomitus of large amounts of free and combined chloride.

According to Close[103] the body, in relationship to its water content, may be divided into three distinct groups:-

(a) Body fluids (extra-cellular) containing 90-99% water.

(b) Nuclear or cellular tissue containing 76-85% "

(c) Matrix or supporting tissue containing 10-73% "

He also states that tissues with many nuclei contain more water than those with small numbers.

The average water content of a number of the more important tissues, estimated by several observers in adult subjects is shown in Table LXX. The average values for each of the tissues, estimated by different investigators, show remarkable uniformity.

TABLE LXX.

Water Content of Tissues - Adults:

as percentage of weight.

Author	Kidney	Muscle	Heart	Lung	Liver	Brain
Magnus Levy (90)	75.6	72.2	74.8	80.0	60.6	77.9
Robt. Hutchison (95)	-	75.0	-	79.4	75.6	-
Blum & Broun (93)	79.7	73.4	-	-	67.7	82.0 Grey 70.0 White
Engels (104)	82.7	75.6	79.2	78.9	68.3	74.8

In infants, however, McQuarrie (105) has found that the percentage water content of the body varies inversely with the age. At birth the water content amounts to 71-72%, while in adults it is only 58-65% of body weight. This difference undoubtedly explains in part the greater requirements of the infant even in health, and the serious danger of any sudden and severe dehydration. According to this author, in cases of oversupply, the amount of fluid not excreted by the kidneys is probably stored in the interstitial spaces, which serve as adjustable reservoirs and fluctuate in volume according to the needs of the individual.

Present Investigation.

The aim of the present section was to determine whether there are any alterations in the chloride and water content of the tissues in infantile diarrhoea, for, as we know, in these patients large amounts of fluid are lost by the severe vomiting and the frequent loose stools.

The material used for these investigations was a series of sixty seven infants dying from various diseases. The tissues were removed at post-mortem in quantities sufficient for the estimation of both the chloride and water content. This group of cases consisted of the following:-

1.	Miscellaneous control group (meningitis, cerebral haemorrhage etc.)	16 cases,
2.	Infantile diarrhoea.	16 cases,
3.	Infantile diarrhoea with broncho pneumonia	10 cases,
4.	Pneumonia and Empyema	11 cases,
5.	Peritonitis	3 cases,
6.	? Renal conditions	6 cases,
7.	(Intestinal obstruction, pyloric & atresia	3 cases,
	(Neo-natal anaemias.	2 cases

and were a consecutive series of post-mortem examinations performed by Dr Blacklock in the Pathological Department of the Royal Hospital for Sick Children, Glasgow.

Immediately after the post-mortem examinations, duplicate specimens (a) and (b) averaging 5 grams, were placed in previously-weighed and dry glass containers. The exact weight of each specimen was then noted and the chloride content determined on specimen (a) by means of the silver nitrate method of Van Slyke[44] and expressed in c.cs. $\frac{N}{10}$ Cl. per cent. The second specimen (b) was placed in a special oven maintained at constant temperature, until the weight remained constant. From the initial and final weights the percentage water content was calculated.

(A). <u>Tissue Chloride and Water Content - Various Diseases.</u>

1. <u>Miscellaneous control group</u>. Owing to the fact that no normal values for tissue chloride or water content in infants are published in the literature, it was considered necessary to use the values obtained from a group of untreated miscellaneous cases as control figures.

Examination of these values for chloride (Table LXXI) shows that the lowest content occurs in muscle (skeletal), increasing progressively in liver, cardiac muscle, kidney, brain and, to a maximum in lung. Schnohr[101], however, found the lowest chloride content in muscle, with a sequence through brain, spleen, kidney and skin to the highest in lung, and maintains that these values have been confirmed in man and animals by other investigators. On comparing the present series with Morris and Graham' cases[88] (Table LXXI), it will be at once observed that, except for muscle, the chloride values of the former have a higher content, which is most marked in the case of lung, kidney and heart. These variations are understandable when we consider the diversity of the material used and the fact that tissues removed from different patients suffering from identical diseases show marked variations (Figs.XXVII to XXXII).

TABLE LXXI.

Average Tissue Chloride Content.

c.cs. $\frac{N}{10}$ Cl.

Author	Muscle	Liver	Heart	Kidney	Brain	Lung
Morris & Graham[88]	43.2	36.5	37.7	42.1	48.9	52.4
Miscellaneous cases	38.0	40.6	43.4	47.7	52.3	61.4

It has been demonstrated previously (Part II) that when saline is administered to patients before death, there occurs, possibly as the result of diminished renal function as well as other causes, an increase of blood chloride. For this reason it was considered advisable to study the chloride values of the tissues of infants, to whom saline in one form or another had been administered, under two main headings:-

(a) those receiving saline within three days of death;

(b) those receiving saline before but not within three days of death.

In a consideration first of those miscellaneous cases, to whom saline had been given within three days of death, the remarkable fact is noted that a substantial increase of tissue chloride occurred in muscle. The tissues of kidney, liver and lung, however, show values similar to those of patients who had no saline, while brain and heart show lower values (Table LXXII, Figs. XXVII-XXXII).

TABLE LXXII.

Average Tissue Chloride Content.
in c.cs. $\frac{N}{10}$ Cl.

Treatment	Muscle	Liver	Heart	Kidney	Brain	Lung	Number
No Saline	38.0	40.6	43.4	47.7	52.3	61.4	12
Saline within 3 days	48.3	39.0	37.0	47.9	43.1	61.9	3
Saline not within 3 days	62.1	37.6	40.3	46.3	-	58.4	1

In one case, where saline had been administered during life but not within three days of death, the average chloride value was very much higher in muscle tissue but comparable otherwise (Table LXXII, Figs. XXVII-XXXII). Schnohr[101] has demonstrated an increased retention of chloride in the brain of animals receiving saline before death. His observations have not been confirmed by the findings in this series of infants.

With regard to the water content of untreated cases, it will be noticed that the average values for the various tissues varied between 76.2%, in the case of muscle, and 87.2% in the case of brain. These values are as expected, very much greater than the water content of adult tissues.

TABLE LXXIII.

Average Water Content-Control as % of weight.

Treatment	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
No Saline	76.2	76.6	81.1	80.8	87.2	80.8	12
Saline	77.9	74.5	83.1	82.2	87.0	83.3	4

As the result of saline administration before death, there occurred an increase in the average water content of the lung, kidney, heart and muscle, more marked in some of these tissues than in others, while the liver showed a fall and brain remained constant (Table LXXIII). Engels[104] found that in dogs, following intra-venous injection of isotonic NaCl solution, there was an increase of water content of all tissues and that two thirds of the fluid retained was stored in the muscle and one sixth in the skin. It is interesting to note that in this miscellaneous series, an increase of both the chloride and water of muscle followed saline injections before death.

2. <u>Infantile Diarrhoea.</u> The observations made on the miscellaneous group were taken as the standard with which the average tissue values in diarrhoea etc. could be compared. It was found (Table LXXIV, Figs. XVII-XXXII) that in infantile diarrhoea and vomiting, when no saline had been administered during life, the tissues of muscle, heart, kidney and lung contained smaller amounts of chloride, while brain and liver showed only slight alterations.

TABLE LXXIV.

Average Chloride Content - Infantile Diarrhoea.
in c.cs. $\frac{N}{10}$ Cl.

Type of Case	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
D.& V. No Saline	35.9	39.9	37.5	40.5	51.8	57.5	3
D.& V. Saline	62.3	58.5	53.7	62.1	60.2	70.0	13
Control Group	38.0	40.6	43.4	47.7	52.3	61.4	12

It would thus appear that, notwithstanding the great loss of electrolyte in these patients with infantile diarrhoea, only slight and insignificant losses of chloride occurred from the fixed tissues. The average values in diarrhoea are also high when compared with the chloride values of patients suffering from pyloric stenosis[88], in which a very definite chloropaenia of tissues does exist.

TABLE LXXV.

Average Tissue Chloride - Pyloric Stenosis and Infantile Diarrhoea.

in c.cs.$\frac{N}{10}$ Cl.

Author	Muscle	Liver	Heart	Kidney	Brain	Lung
Morris & Graham[88]	24.6	22.9	16.6	23.0	24.9	30.7
Present Series	35.9	39.9	37.5	40.5	51.8	57.5

As the result of saline administration to these infants within three days of death, a marked increase of chloride in all tissues occurred, but this is most marked in the case of muscle, heart and kidney (Table LXXIV, Figs. XXVII-XXXII). Morris and Graham[88] have also shown that in infants suffering from pyloric stenosis, to whom saline had been administered before death, there occurred a marked increase in the chloride value of all tissues, the average for the series exceeding the averages obtained for the control group of patients. Further, it is significant that, with the possible exception of peritonitis cases, this fixation of chloride in the tissues of infantile diarrhoea patients receiving saline injections is more marked than in patients dying from pneumonia or infantile diarrhoea and pneumonia (see later).

In diarrhoeal infants receiving no fluid, the tissue water content was only slightly lower in muscle, heart and liver than was found in the miscellaneous control group (Table LXXVI). The deficiencies in these tissues, however, with the possible exception of liver, do not appear significant nor do they support the findings of Hamilton and Schwartz[106] that, as the result of water deprivation in dogs, a marked loss of extra-cellular water occurs from muscle tissue.

TABLE LXXVI.

Average Water Content - Controls and Diarrhoea.

as percentage

Type of Case	Muscle	Liver	Heart	Kidney	Brain	Lung
Controls	76.2	76.6	81.1	80.8	87.2	80.8
D. & V. No Saline	75.1	73.8	80.3	80.1	86.4	80.3
D. & V. Saline	78.7	76.5	81.5	82.0	87.4	80.7

As the result of saline administration before death, a marked increase in the percentage water content of all tissues, except lung, occurred. This increase is more significant in the case of muscle than in heart or brain tissue (Table LXXVI).

It thus appears that in infants suffering from the effects of infantile diarrhoea, there occurs an increase of both chloride and water in most of the tissues as the result of saline administration. Von Moraczewski[94] has maintained that, in all cases where chloride is retained, water is also retained and serves to form with it an isotonic solution. This view has not been confirmed by the work of Hutchison[95] Padtberg[107],[108] et alii[85] who have demonstrated a "dry retention" of chloride in the body after saline administration.

TABLE LXXVII.

Average Tissue Increase - after Saline: Diarrhoea.

Muscle	Kidney	Heart	Brain	Lung	Liver	
26.4	21.6	16.2	8.4	12.5	18.6	c.cs. N/10 Cl.
3.6	1.9	1.2	1.0	0.4	2.7	water %

Table LXXVII clearly demonstrates that, in the tissues of saline-treated patients dying from infantile diarrhoea, a "dry retention" of chloride does occur in some of the tissues.

3. Infantile Diarrhoea with Broncho-pneumonia. In this group the chloride content of all the tissues, with the exception of liver which appears high, showed values in close relationship to those of the control group (Table LXXVIII).

TABLE LXXVIII.

Average Tissue Chloride - Control and Diarrhoea with Pneumonia in c.cs.N/10 Cl.

Type of Case	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
Control Cases	38.0	40.6	43.4	47.7	52.3	61.4	12
D.& Pn. No Saline	40.5	50.7	42.0	50.5	46.9	61.3	7
D.& Pn. Saline 3 days.	66.5	55.4	45.7	53.9	53.7	64.7	2
D.& Pn. No Saline 3 days.	55.7	48.3	38.4	48.8	46.7	52.8	1

The effect of saline administration, within a period of three days of death, in these patients was a small increase of chloride in all tissues, most marked in the muscle (Table LXXVIII, Figs. XXVII-XXXII). The increased fixation is, however, not as marked as in saline-treated patients dying from infantile diarrhoea and vomiting without pneumonia (Table LXXIV, Figs. XXVII-XXXII).

In the one patient suffering from diarrhoea with bronchopneumonia, to whom no saline had been given during the last three days of life, the average chloride values of liver, kidney, heart and brain were similar to the values found in patients who had never received saline. The content of muscle was still raised and that of the lung much lowered (Table LXXVIII). As has been previously mentioned the tissue variations in different cases are so great that the results estimated for only one may not be of very great significance.

The average water content of these tissues exhibited values in close agreement with those of control infants (Table LXXIX).

TABLE LXXIX.

Average Water Content - Control and Diarrhoea - Pneumonia. as Percentage.

Type of Case	Muscle	Liver	Heart	Kidney	Brain	Lung
Controls	76.2	76.6	81.1	80.8	87.2	80.8
D. & Pn.	75.4	77.7	81.7	80.3	85.2	80.5
D. & Pn. (Saline)	78.9	78.2	82.2	81.8	86.6	81.2

As the result of saline injections, however, a slight increase occurred in the tissue water of liver, kidney, brain and muscle, the increase being most marked in muscle (Table LXXIX).

4. Broncho-Pneumonia. It has been mentioned that von Moraczewski[94] et alii[95][96] found an increase in the chloride content of all tissues of adults dying from lobar pneumonia. The observation aroused curiosity as to whether a similar increase would be met with in infants dying from broncho-pneumonia.

TABLE LXXX.

Average Tissue Chloride - Broncho-Pneumonia

in c.cs. $\frac{N}{10}$ Cl.

Type of Case	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
Controls	38.0	40.6	43.4	47.7	52.3	61.4	12
Br.-Pn.	43.5	43.5	44.5	49.2	43.2	67.9	8
Br.-Pn.(Saline)	59.1	50.7	49.0	51.2	50.5	69.3	3

The average tissue chloride figures of these patients (Table LXXX, Figs. XXVII-XXXII), as compared with the control series, show that in all tissues, except that of brain, a slight increase in the average value occurred. In the case of brain tissue, however, the average was much lower than the "normal" content. The lungs showed rather high values, which is not at all surprising when the nature of the disease is considered.

As the result of saline administration during life to these infants, a marked increase in the average chloride value was found in the tissues of liver, brain and muscle with a smaller increase in lung, kidney and heart (Table LXXX, Figs. XXVII-XXXII).

The average tissue percentage of water in these infants was similar to that found in the miscellaneous control group, some figures being raised and others lowered a little. In the case of muscle and brain, the average water content in pneumonia was definitely lower than in the controls. This was unexpected and is at variance with the results of Hutchison[95], who found an increased water content of tissues in adults dying from primary pneumonia.

TABLE LXXXI.

Average Water Content - Broncho-Pneumonia: as percentage.

Type of Case	Muscle	Liver	Heart	Kidney	Brain	Lung
Controls	76.2	76.6	81.1	80.8	87.2	80.8
Br.-Pn.	73.9	74.9	79.7	81.5	85.5	81.6
Br.-Pn.(Saline)	72.6	75.7	80.8	80.8	-	80.9

As the result of saline injections, a slight increase in the water percentage was found in heart and liver with a slight fall in muscle, kidney and lung. These variations do not appear to be significant (Table LXXXI).

5. <u>Peritonitis</u>. In two patients dying from peritonitis a diminished chloride content was noted in the brain, heart and kidney, while the other tissues exhibited values either above or similar to those of the control group (Table LXXXII).

As the result of saline injections before death, in one infant, there was a chloride increase in all the tissues examined, but most marked in kidney, liver and lung (Table LXXXII, Figs. XXVII-XXXII)

TABLE LXXXII.

Average Tissue Chloride - Peritonitis.

In c.cs. $\frac{N}{10}$ Cl.

Type of Case	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
Controls	38.0	40.6	43.4	47.7	52.3	61.4	12
Peritonitis	43.6	46.0	38.6	39.6	45.9	59.0	2
" (Saline)	55.0	62.6	42.5	61.7	-	79.1	1

Whether these alterations, in such a small group of cases, can be considered significant is debatable; nevertheless some of the tissue chloride increases in peritonitis after saline administration appear nearly as marked as those in diarrhoeal infants. It might thus tentatively be suggested that factors, resulting in an increased fixation of chloride in the tissues, are operative in both these conditions.

The water content of the tissues in two cases of peritonitis was comparable with the control group. The other, which had been given saline, showed large increases in the percentage water of lung, muscle and liver (Table LXXXIII).

TABLE LXXXIII.

Average Water Content - Peritonitis.

as percentage.

Type of Case	Muscle	Liver	Heart	Kidney	Brain	Lung
Controls	76.2	76.6	81.2	80.8	87.2	80.8
Peritonitis	76.9	74.9	82.4	80.8	87.5	79.6
" (Saline)	80.0	78.2	81.4	82.2	-	87.3

6. Renal Cases. The cases under this heading were not true cases of nephritis, but infants suffering from such conditions as hydronephrosis and pyelo-nephritis.

The average chloride content of the tissues, in a patient who had no saline before death, was markedly raised in kidney and muscle, but similar to the control in lung and heart. It seems desirable to suspend comment on these findings until a number of similar infants can be examined. The high chloride content of kidney tissue in this patient should however be noted.

As the result of injections of saline, very confusing and variable deviations of tissue chloride occurred (Table LXXIV, Figs. XXVII-XXXII).

TABLE LXXXIV.

Average Chloride Content - Renal Cases.

In c.cs. $\frac{N}{10}$ Cl.

Type of Case	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
Controls	38.0	40.6	43.4	47.7	52.3	61.4	12
Renal, no Saline	55.0	-	45.9	62.0	-	57.5	1 *
" Saline 3 days.	46.9	42.0	47.0	54.8	51.7	68.3	4
" no Saline 3 days.	41.5	55.9	43.1	60.0	43.2	60.0	1

* ?? Acute Nephritis.

The percentage water content also showed marked variations, high figures for muscle, lung and kidney tissues and slightly raised values in the heart. The effect of saline administration before death was also variable, the most common finding being a fall in the water content (Table LXXXV).

TABLE LXXXV.

Average Water Content - Renal Cases.

as percentage.

Type of Case	Muscle	Liver	Heart	Kidney	Brain	Lung
Controls	76.2	76.6	81.2	80.8	87.2	80.8
Renal	82.7	-	83.2	86.9	-	85.9 *
" (Saline)	78.0	75.3	81.4	79.9	85.2	80.7

* ?? Acute Nephritis (one case only)

It should be noted that Blum et alii[109] have also demonstrated an increased water content in muscle, liver and kidney tissues of adults dying from uraemia.

7. Pyloric Stenosis, Atresia of Bowel and Neo-Natal Anaemia. The average chloride values in patients dying as the result of bowel obstructions were rather low but did not reach the low levels found by Graham and Morris[88] in a similar series. The values in two cases of neo-natal anaemia, which had been transfused, showed only slight and unimportant variations when compared with the control observations (Table LXXXVI).

TABLE LXXXVI.

Average Chloride Content - Intest. Obstr. and Anaemia.

in c.cs.N/10 Cl.

Type of Case	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
Controls	38.0	40.6	43.4	47.7	52.3	61.4	12
Obstruction	42.1	44.6	37.9	46.1	-	47.0	3
Anaemia	49.0	53.8	49.5	57.9	65.8	64.9	2

TABLE LXXXVII.

Average Water Content - Intest. Obstruction and Anaemia.

as percentage

Type of Case	Muscle	Liver	Heart	Kidney	Brain	Lung
Controls	76.2	76.6	81.2	80.8	87.2	80.8
Obstruction	81.4	77.6	82.4	81.5	-	81.3
Anaemia	77.7	74.8	79.9	78.7	87.4	77.0

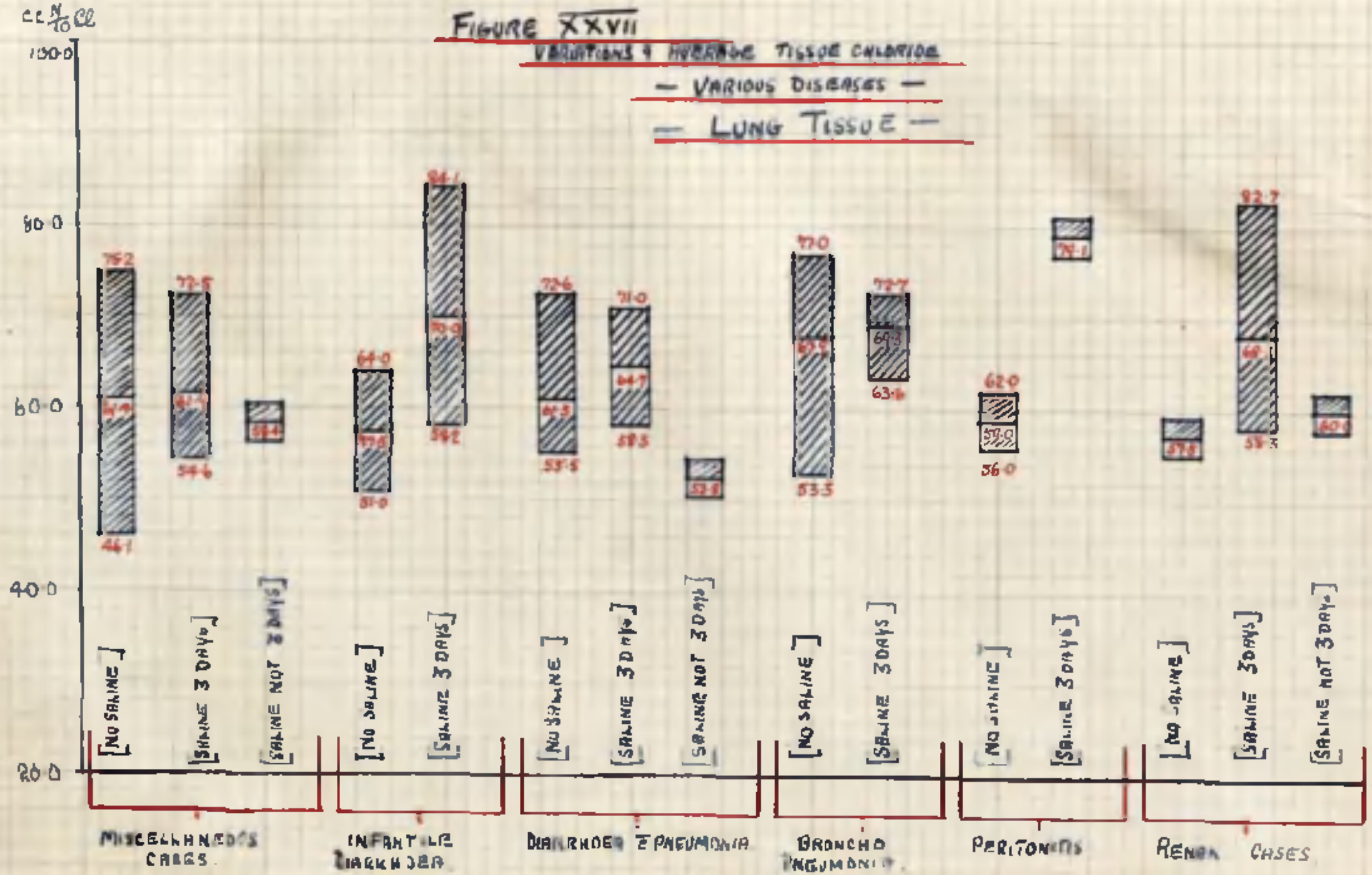


Figure XXVII
Variations & Average Tissue Chloride
— Various Diseases —
— Lung Tissue —

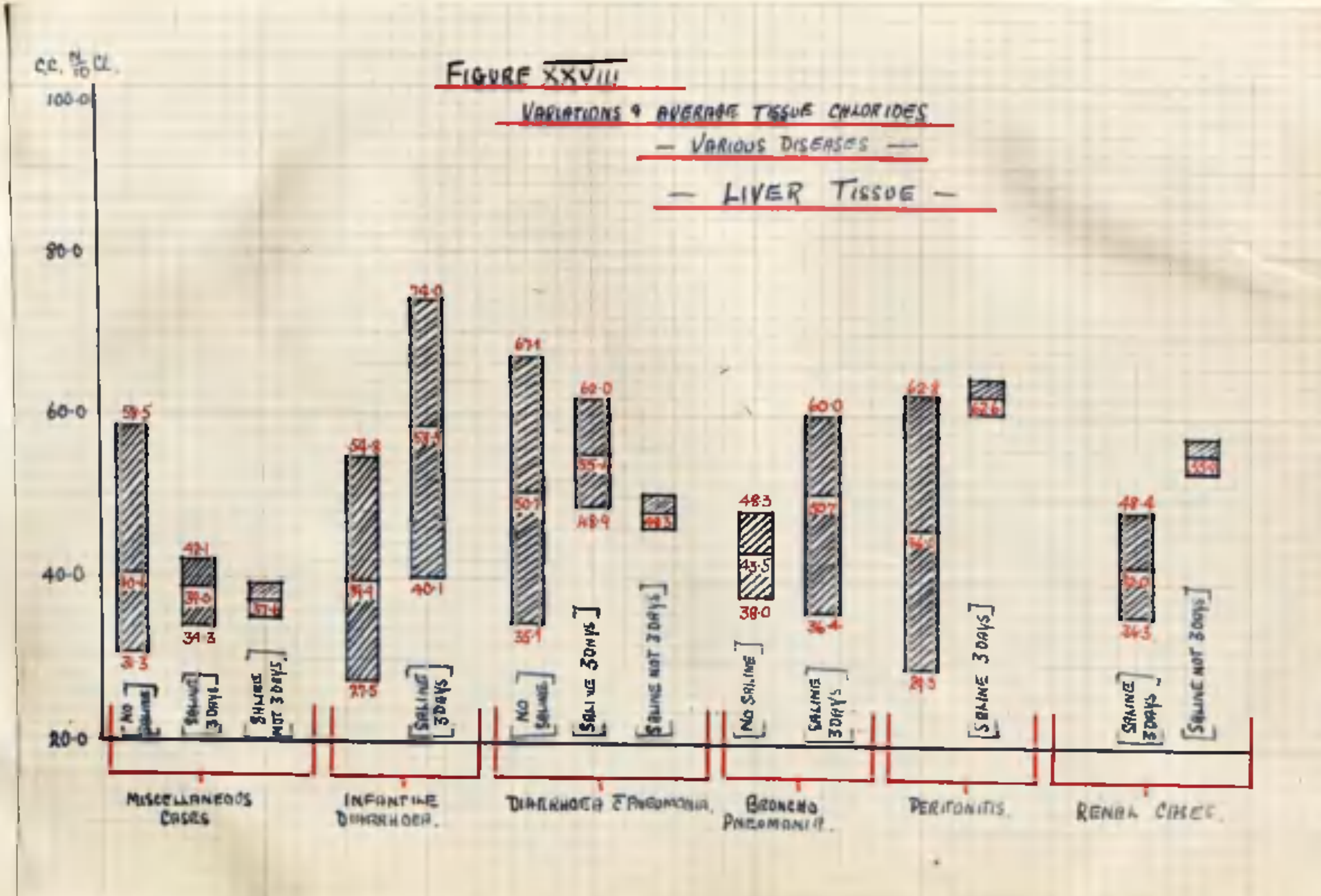


FIGURE XXVIII
VARIATIONS & AVERAGE TISSUE CHLORIDES
— VARIOUS DISEASES —
— LIVER TISSUE —
cc. N/10 Cl.
100·0
80·0
60·0
40·0
20·0
59·5
40·4
31·3
42·1
34·3
54·8
27·5
74·0
40·1
67·1
50·7
35·1
60·0
55·4
48·9
48·3
45·5
38·0
60·0
50·7
36·4
62·8
28·5
48·4
34·3
NO SALINE
SALINE 3 DAYS
SALINE NOT 3 DAYS
SALINE 3 DAYS
NO SALINE
SALINE 3 DAYS
SALINE NOT 3 DAYS
NO SALINE
SALINE 3 DAYS
SALINE 3 DAYS
SALINE 3 DAYS
SALINE NOT 3 DAYS
MISCELLANEOUS CASES
INFANTILE DIARRHOEA.
DIARRHOEA & PNEUMONIA.
BRONCHO PNEUMONIA.
PERITONITIS.
RENAL CASES.

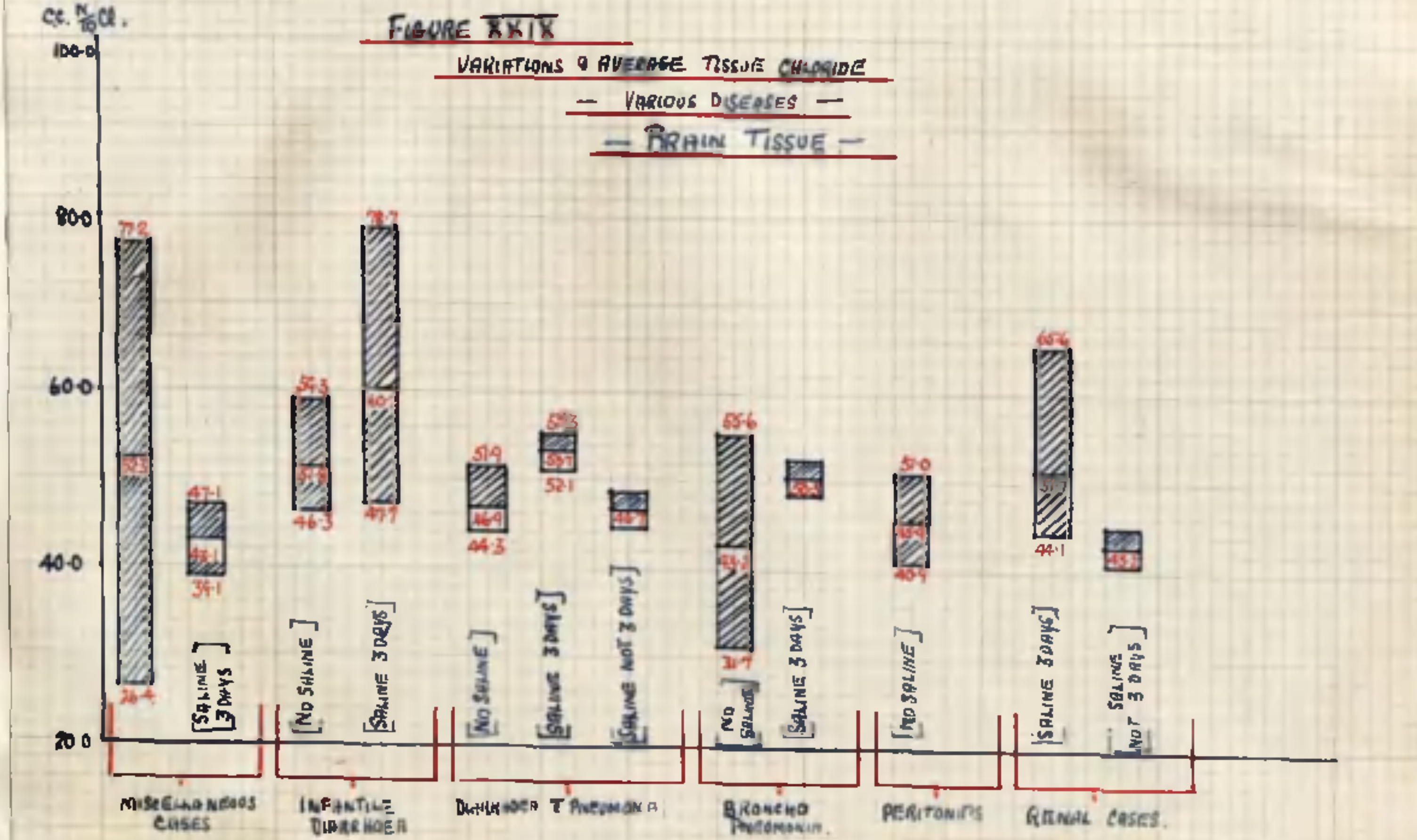


FIGURE XXIX
VARIATIONS OF AVERAGE TISSUE CHLORIDE
— VARIOUS DISEASES —
— BRAIN TISSUE —
cc. N/10 Cl.
100·0
80·0
60·0
40·0
20·0
MISCELLANEOUS CASES
INFANTILE DIARRHOEA
DIARRHOEA & PNEUMONIA
BRONCHO PNEUMONIA.
PERITONITIS
RENAL CASES.
[SALINE 3 DAYS]
[NO SALINE]
[SALINE 3 DAYS]
[NO SALINE]
[SALINE 3 DAYS]
[SALINE NOT 3 DAYS]
[NO SALINE]
[SALINE 3 DAYS]
[NO SALINE]
[SALINE 3 DAYS]
[SALINE NOT 3 DAYS]

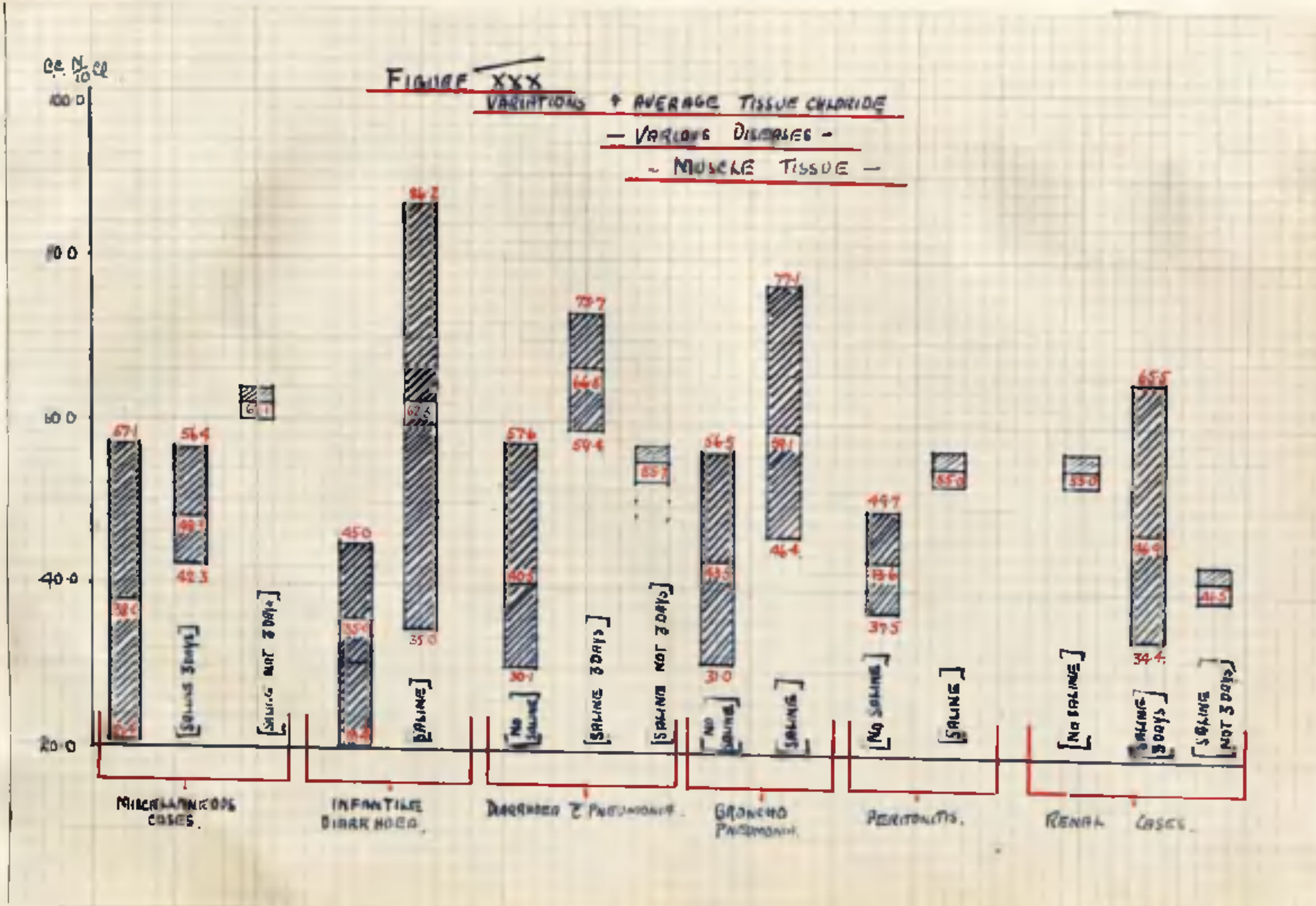


Figure XXX
Variations of Average Tissue Chloride
– Various Diseases –
– Muscle Tissue –
cc. N/10 Cl
100.0
80.0
60.0
40.0
20.0
57.1
56.4
42.3
45.0
86.2
35.0
57.6
30.1
73.7
59.4
56.5
31.0
77.1
46.4
49.7
37.5
65.5
34.4
[Saline 3 days]
[Saline not 3 days]
[Saline]
[No Saline]
[Saline 3 days]
[Saline not 3 days]
[No Saline]
[Saline]
[No Saline]
[Saline]
[No Saline]
[Saline 3 days]
[Saline not 3 days]
Miscellaneous Cases.
Infantile Diarrhoea.
Diarrhoea ē Pneumonia.
Broncho Pneumonia.
Peritonitis.
Renal Cases.

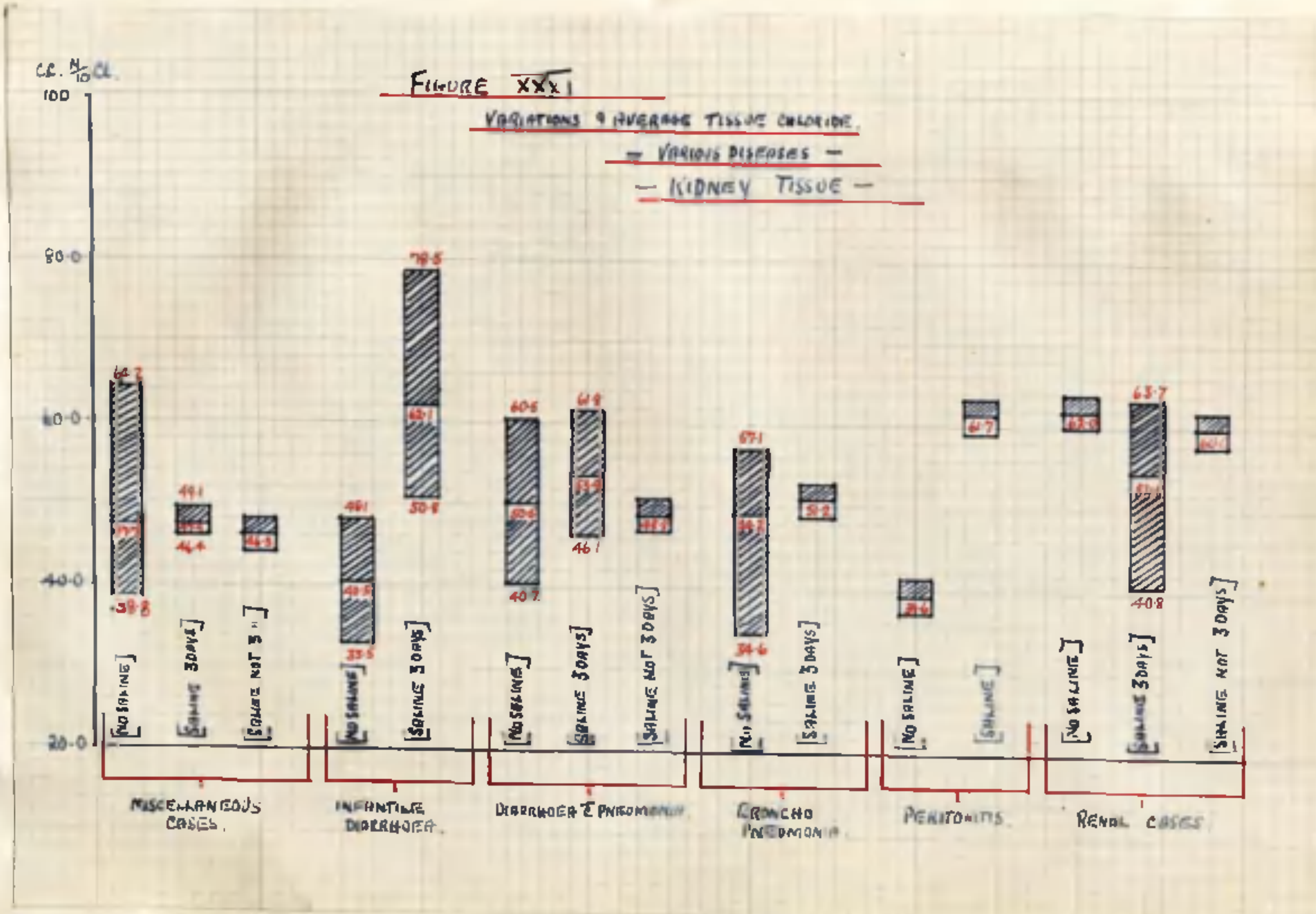


FIGURE XXXI
VARIATIONS IN AVERAGE TISSUE CHLORIDE.
— VARIOUS DISEASES —
— KIDNEY TISSUE —
CC. N/10 Cl.
100
80·0
60·0
40·0
20·0
64·2
39·8
49·1
46·4
49·1
33·5
78·5
50·8
60·6
40·7
61·8
46·1
67·1
34·6
63·7
40·8
[NO SALINE]
[SALINE 3 DAYS]
[SALINE NOT 3 "]
[SALINE NOT 3 DAYS]
[SALINE]
MISCELLANEOUS CASES.
INFANTILE DIARRHOEA.
DIARRHOEA & PNEUMONIA.
BRONCHO PNEUMONIA.
PERITONITIS.
RENAL CASES.

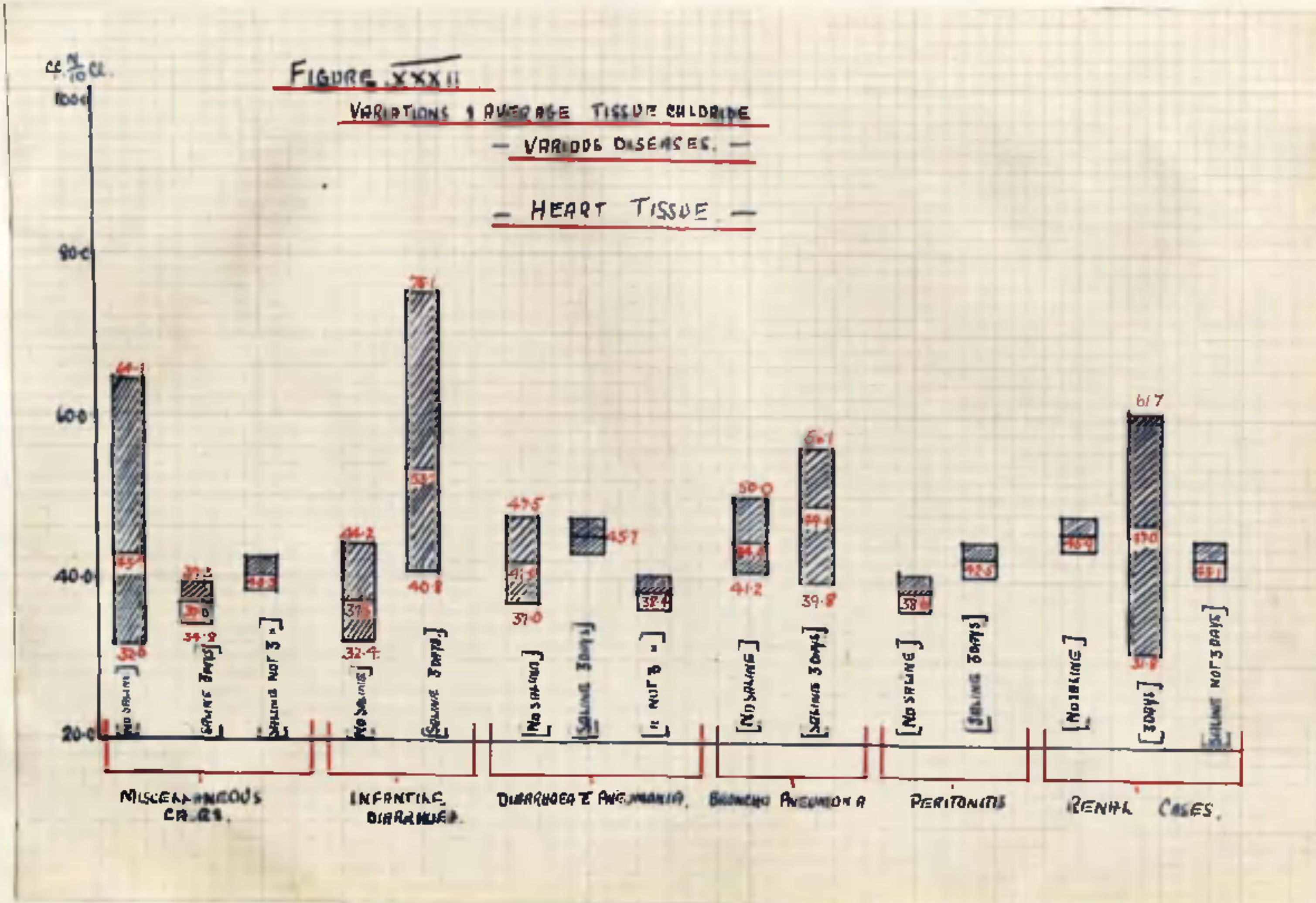


FIGURE XXXII

VARIATIONS IN AVERAGE TISSUE CHLORIDE

— VARIOUS DISEASES. —

— HEART TISSUE —

(B). Relationship of Chloride and Water Content to Age.

Rominger et alii[110] *have stated that the younger* the infant, the greater is its capacity for storing chloride, while McQuarrie[105] has demonstrated that the water content of brain tissue varies inversely with age. In an attempt to discover whether these statements could be substantiated, it was considered necessary to examine the chloride and the water contents of various infantile tissues in relationship to age. For this purpose the age grouping employed was :-

(a) 0 - 1 month

(b) 1 - 3 months

(c) 3 - 6 months

(d) *over 6 months.*

The tabulated values for the group of miscellaneous infants, which have previously been considered as the standard for comparison (Table LXXXVIII), show no apparent relationship between the age group and the chloride content of the tissues.

TABLE LXXXVIII.

Chloride Content - Age: Miscellaneous Cases.

in c.cs. $\frac{N}{10}$ Cl.

Age - mths.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
0 - 1	37.7	42.1	40.2	44.4	58.0	54.6	4
1 - 3	49.9	51.4	54.3	55.4	50.0	62.5	2
3 - 6	35.1	47.2	46.0	54.7	53.8	75.2	1
over 6	34.2	34.6	41.0	45.9	50.3	63.7	5

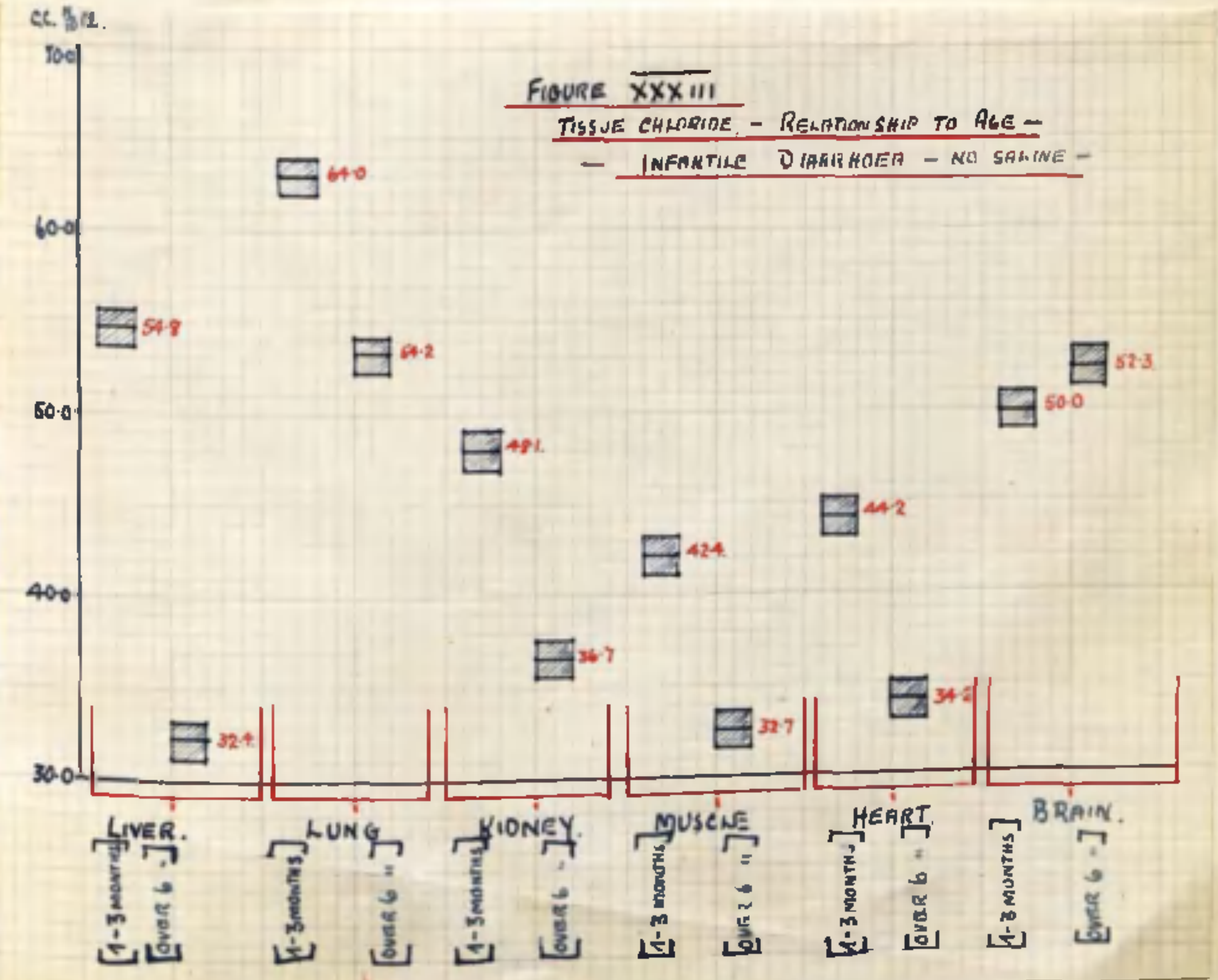
Unfortunately only three cases of infantile diarrhoea to which no saline had been given, present themselves for examination.

TABLE LXXXIX.

Chloride Content - Age: Infantile Diarrhoea.

in c.cs. $\frac{N}{10}$ Cl.

Age - mths.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
0 - 1	-	-	-	-	-	-	-
1 - 3	42.4	54.8	44.2	48.1	50.0	64.0	1
3 - 6	-	-	-	-	-	-	-
over 6	32.7	32.4	34.2	36.7	52.3	54.2	2



and in these, all tissues except brain appear to shew that the younger infants have a very high chloride content. No generalisation, however, can be made from three cases (Table LXXXIX; Fig. XXXIII).

TABLE XC.

Chloride Content - Age: Diarrhoea with Pneumonia.

in c.cs. $\frac{N}{10}$ Cl.

Age - mths.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
0 - 1	-	-	-	-	-	-	-
1 - 3	41.4	45.8	40.3	47.5	44.3	59.9	2
3 - 6	44.5	52.6	45.4	55.0	48.4	58.0	2
over 6	37.3	51.1	42.1	49.5	47.5	64.4	3

TABLE XCI.

Chloride Content - Age: Broncho-pneumonia.

In c.cs. $\frac{N}{10}$ Cl.

Age - mths.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
0 - 1	-	-	-	-	-	-	-
1 - 3	48.6	47.0	43.9	47.2	55.6	60.4	2
3 - 6	51.4	43.8	43.8	42.6	50.3	69.2	2
over 6	36.9	31.6	45.2	53.6	36.7	71.2	4

In the other groups, infantile diarrhoea with broncho-pneumonia, and broncho-pneumonia solely, examination of the tabulated results (Tables XC and XCI) again fails to indicate any relationship between age and tissue chloride content.

TABLE XCII.

Water Content - Age: Miscellaneous Group.

as percentage

Age - mths.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
0 - 1	79.2	76.5	82.3	79.6	89.3	79.9	4
1 - 3	75.0	76.7	80.4	79.9	87.3	81.2	2
3 - 6	74.7	77.3	82.2	81.4	86.7	79.6	1
over 6	74.6	76.5	80.6	82.4	84.7	81.8	5

On examination of the percentage water content in the miscellaneous group (Table XCII), it will be seen that only the tissues of muscle and brain gave evidence of a greater water content in the younger infants. The remainder of the tissues showed only minor variations.

TABLE XCIII.

Water Content - Age: Infantile Diarrhoea.

as percentage

Age - mths.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
0 - 1	-	-	-	-	-	-	-
1 - 3	80.8	77.7	82.5	85.3	90.2	81.2	1
3 - 6	-	-	-	-	-	-	-
over 6	72.3	71.8	79.2	77.5	84.5	79.9	2

In the three patients dying from infantile diarrhoea, however, all tissues examined showed appreciably higher values in the younger infants (Table XCIII). This was also found in cases suffering from infantile diarrhoea with associated broncho-pneumonia (Table XCIV).

TABLE XCIV.

Water Content - Age: Diarrhoea with Pneumonia.

as percentage

Age - mths.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
0 - 1	-	-	-	-	-	-	-
1 - 3	79.4	80.8	84.5	83.5	92.2	83.7	2
3 - 6	76.0	76.9	80.4	81.3	85.0	80.8	2
over 6	74.6	77.8	81.3	78.8	85.2	80.2	3

TABLE XCV.

Water Content - Age: Broncho-pneumonia.

as percentage

Age - mths.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
0 - 1	-	-	-	-	-	-	-
1 - 3	78.5	78.3	82.6	81.7	87.5	83.5	2
3 - 6	69.1	76.3	78.3	82.3	86.8	78.9	2
over 6	74.1	72.6	78.9	81.1	84.3	82.1	4

In the cases suffering from broncho-pneumonia alone, there was also noted a tendency for the highest figures to be found in the youngest children, but the differences were not striking. Moreover, the differences being small and the cases few, it would be unwise to assume any definite relationship to age (Table XCV).

It is thus impossible from these results to state definitely whether any relationship exists between the tissue chloride or water content and the age of the infant, but some such association is suggested by certain tissues, in various groups of cases, showing appreciably greater values in the younger children.

<u>Saline Administration</u>. Rominger's[110] suggestion that the capacity to store chloride decreased with age prompted an examination of the findings in the present series. The miscellaneous control group, receiving saline before death, showed no definite increased power for such fixation in the tissues of the younger infants. In the 3 to 6 month period, liver and heart exhibited slightly higher values, while in the oldest category lung, kidney and muscle showed greater concentrations (Table XCVI).

TABLE XCVI.

Chloride Content - Age: Miscellaneous Cases.

in c.cs. $\frac{N}{10}$ Cl.

Age - mths.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases.
0 - 1	-	-	-	-	-	-	-
1 - 3	-	-	-	-	-	-	-
3 - 6	42.3	40.7	39.3	46.4	-	54.6	1
over 6	51.3	38.2	34.8	48.7	43.1	65.6	2

TABLE XCVII.

Chloride Content - Age: Diarrhoea.

in c.cs. $\frac{N}{10}$ Cl.

Age - mths.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases.
0 - 1	69.8	65.8	52.6	68.4	62.6	74.5	4
1 - 3	68.2	63.4	56.2	63.2	62.2	69.1	4
3 - 6	57.9	48.4	49.7	54.7	56.5	69.5	4
over 6	48.2	40.1	40.8	50.8	-	58.8	1

In the case of patients dying from the effects of infantile diarrhoea, there did, however, appear to be an increased power for the fixation of chloride by some of the

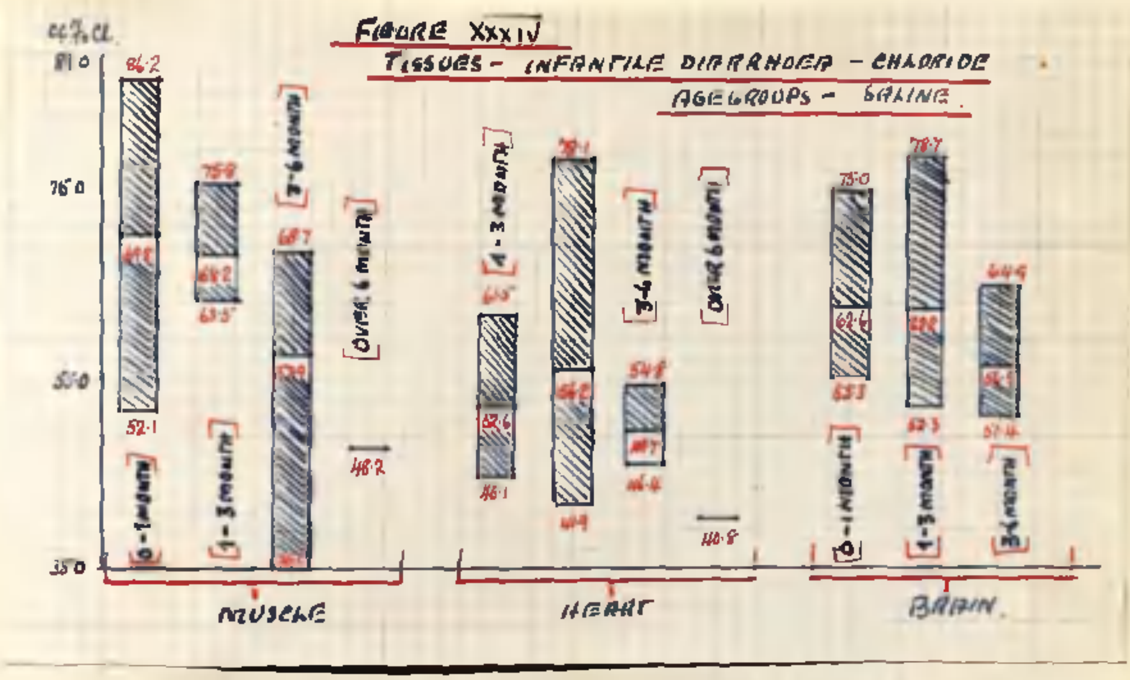


FIGURE XXXIV
TISSUES - INFANTILE DIARRHOEA - CHLORIDE
AGEGROUPS - SALINE.
0-1 MONTH
1-3 MONTH
3-6 MONTH
OVER 6 MONTH
MUSCLE
HEART
BRAIN.

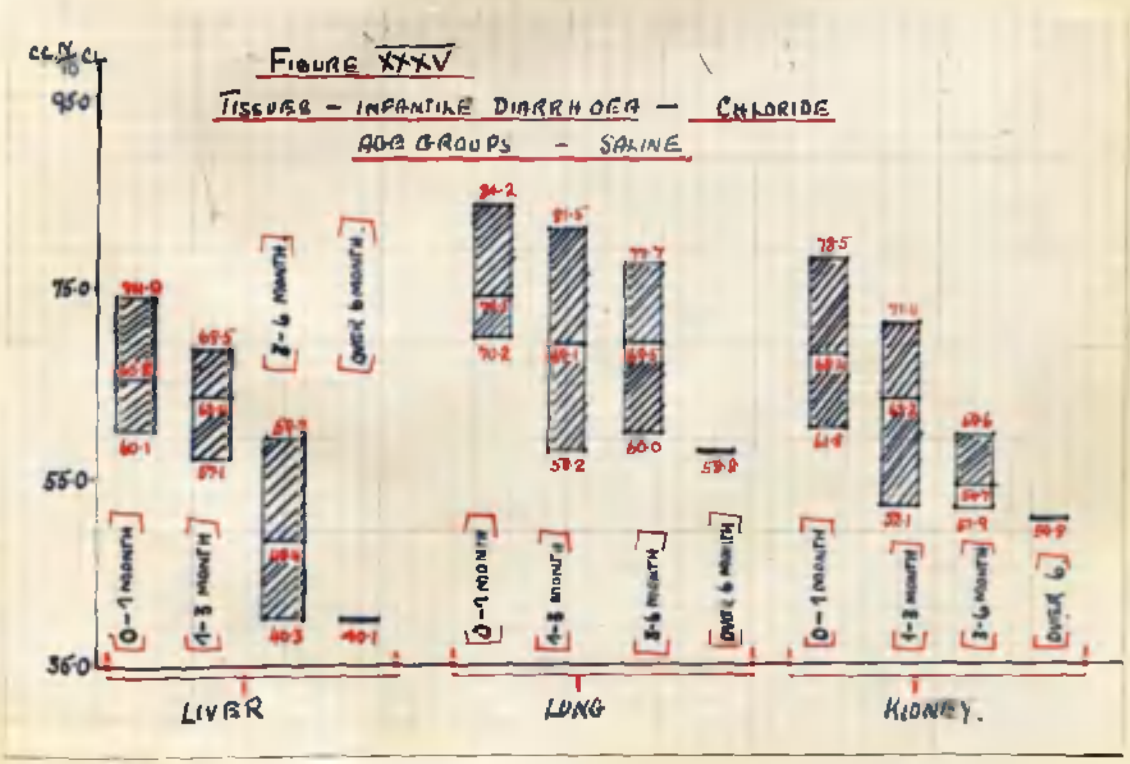


FIGURE XXXV
TISSUES - INFANTILE DIARRHOEA - CHLORIDE
AGE GROUPS - SALINE
95.0
75.0
55.0
36.0
0-1 MONTH
1-3 MONTH
3-6 MONTH
OVER 6 MONTH.
LIVER
LUNG
KIDNEY.

tissues, in the younger patients. The increase is most striking in the first trimester and, though demonstrable, is much less obvious in the later periods (Table XCVII, Figs. XXXIV and XXXV).

TABLE XCVIII.

Chloride Content - Age: Diarrhoea with Pneumonia.

in c.cs. $\frac{N}{10}$Cl.

Age - mths.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
0 - 1	-	-	-	-	-	-	-
1 - 3	73.7	62.0	45.1	61.8	55.3	71.0	1
3 - 6	-	-	-	-	-	-	-
over 6	57.5	48.6	42.3	47.4	49.4	55.5	2

In three cases suffering from infantile diarrhoea with broncho-pneumonia, it will be readily observed that the chloride content in the youngest child greatly exceeded that of similar tissues in the higher age group (Table XCVIII).

TABLE XCIX.

Water Content - Age: Miscellaneous Group.

as percentage

Age - mths.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
0 - 1	-	-	-	-	-	-	-
1 - 3	-	-	-	-	-	-	-
3 - 6	75.1	75.3	81.3	81.4	-	84.5	1
over 6	73.8	71.2	81.6	80.8	86.9	81.2	2

In an examination of the average water content of the tissues after saline injection in the miscellaneous control group, there does appear to be a greater retention of water in most of the tissues of the youngest infant (Table XCIX, Figs. XXXVI-XLI).

TABLE C.

Water Content - Age: Diarrhoea.

as percentage.

Age - mths.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
0 - 1	82.1	79.1	82.0	83.2	87.7	82.5	4
1 - 3	79.7	79.9	82.3	82.7	88.4	82.0	4
3 - 6	75.7	75.3	80.6	79.6	86.1	78.7	4
over 6	78.8	74.8	81.4	82.3	-	77.7	1

Rather similar findings were noted in the cases of infantile diarrhoea, particularly in the tissues of liver, lung and muscle although the values of brain, heart and kidney also show slight variations. The general tendency is for an increased water content to be present in the tissues of the younger infants (Table C, Figs. XXXVI-XLI).

Practically identical observations were made in patients dying as the result of infantile diarrhoea with broncho-pneumonia, and although the number of cases comprising this group is small, these results taken in conjunction with the findings in the other groups, appear significant (Table CI, (Figs. XXXVI-XLI).

TABLE CI.

Water Content - Age: Diarrhoea with Pneumonia.

as percentage.

Age - mths.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
0 - 1	-	-	-	-	-	-	-
1 - 3	80.3	79.6	82.4	83.3	88.1	82.3	1
3 - 6	-	-	-	-	-	-	-
over 6	78.0	77.4	82.0	81.2	85.6	80.4	2

These results thus indicate that, generally speaking, an increased retention of chloride and water does occur in most tissues following saline administration and is more marked in the case of the younger infant. The numbers examined and the age distribution does not justify a more definite statement.

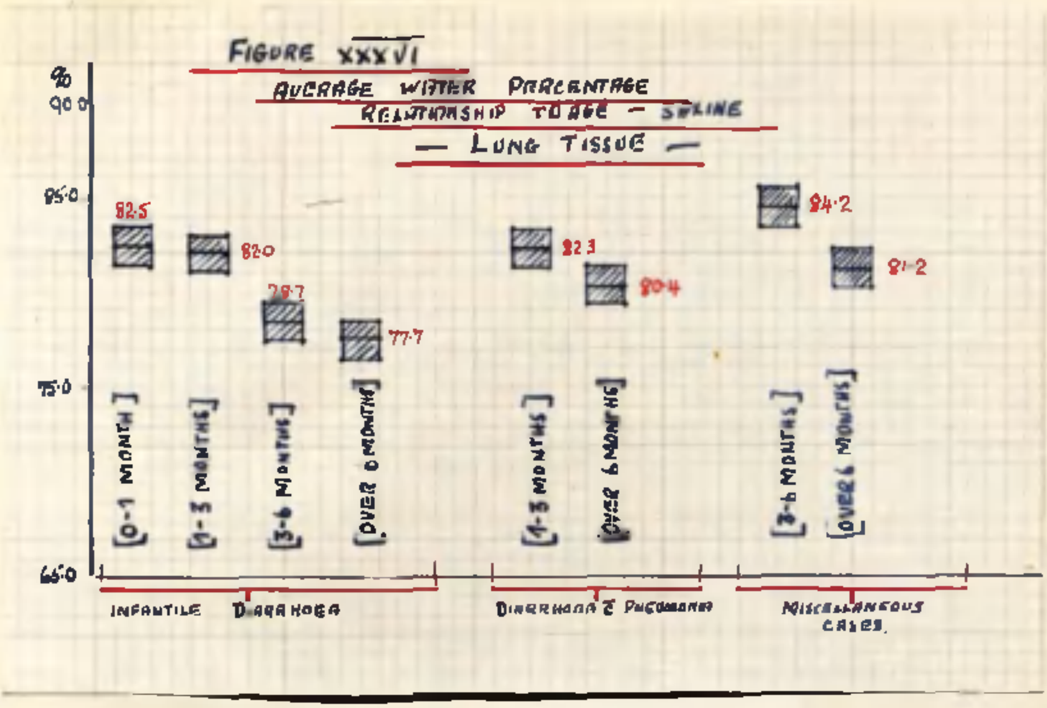
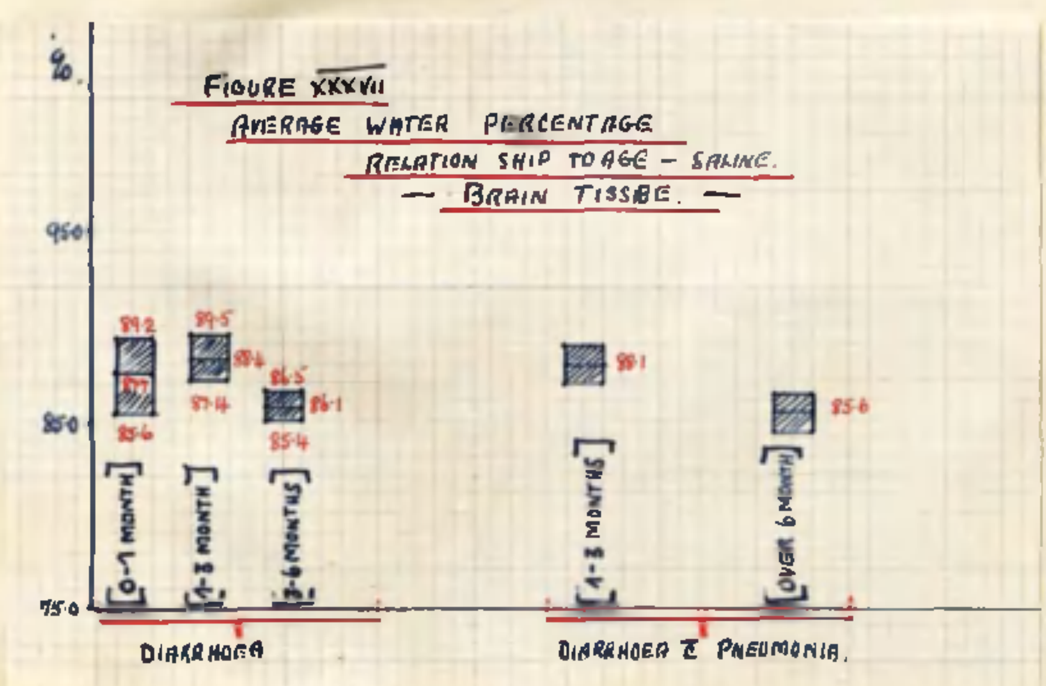


FIGURE XXXVI
AVERAGE WATER PERCENTAGE
RELATIONSHIP TO AGE - SALINE
— LUNG TISSUE —
%
90.0
85.0
75.0
65.0
82.5
82.0
78.7
77.7
82.3
80.4
84.2
81.2
[0-1 MONTH]
[1-3 MONTHS]
[3-6 MONTHS]
[OVER 6 MONTHS]
[1-3 MONTHS]
[OVER 6 MONTHS]
[3-6 MONTHS]
[OVER 6 MONTHS]
INFANTILE DIARRHOEA
DIARRHOEA C̄ PNEUMONIA
MISCELLANEOUS CASES.


%
FIGURE XXXVII
AVERAGE WATER PERCENTAGE
RELATION SHIP TO AGE - SALINE.
— BRAIN TISSUE. —
95.0
85.0
75.0
89.2
85.6
89.5
88.4
87.4
86.5
86.1
85.4
88.1
85.6
[0-1 MONTH]
[1-3 MONTH]
[3-6 MONTHS]
[1-3 MONTHS]
[OVER 6 MONTHS]
DIARRHOEA
DIARRHOEA C̄ PNEUMONIA.

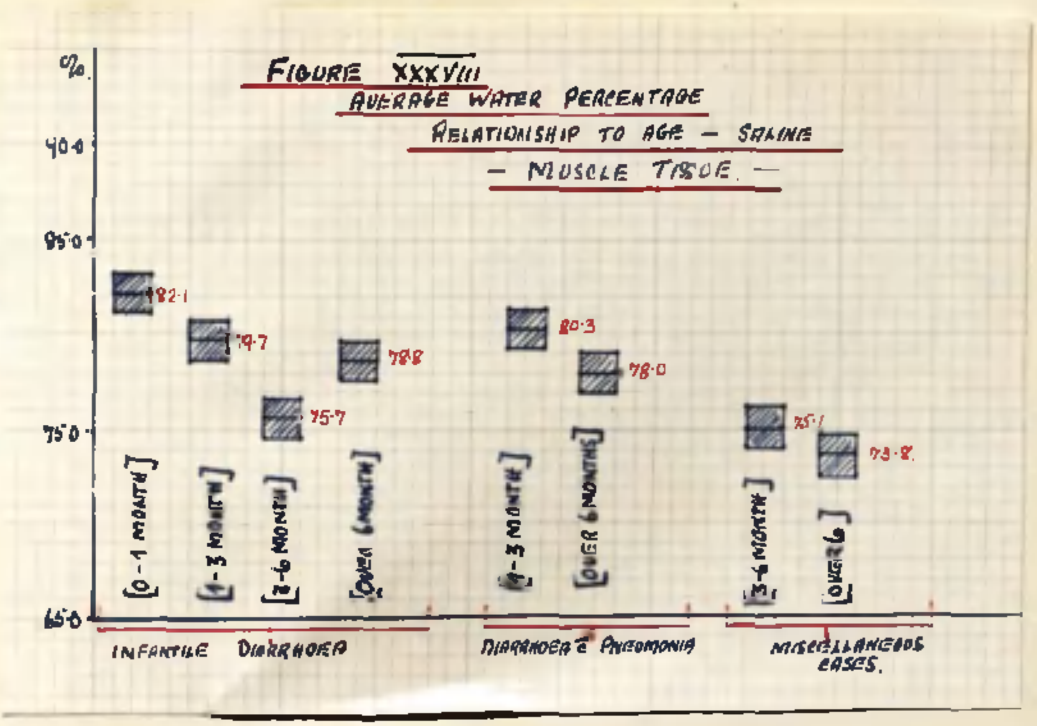


FIGURE XXXVIII
AVERAGE WATER PERCENTAGE
RELATIONSHIP TO AGE — SALINE
— MUSCLE TISSUE. —
%.
90·0
85·0
75·0
65·0
82·1
79·7
75·7
78·8
80·3
78·0
75·1
73·8
[0-1 MONTH]
[1-3 MONTH]
[3-6 MONTH]
[OVER 6 MONTH]
[1-3 MONTH]
[OVER 6 MONTHS]
[3-6 MONTH]
[OVER 6]
INFANTILE DIARRHOEA
DIARRHOEA c̄ PNEUMONIA
MISCELLANEOUS CASES.

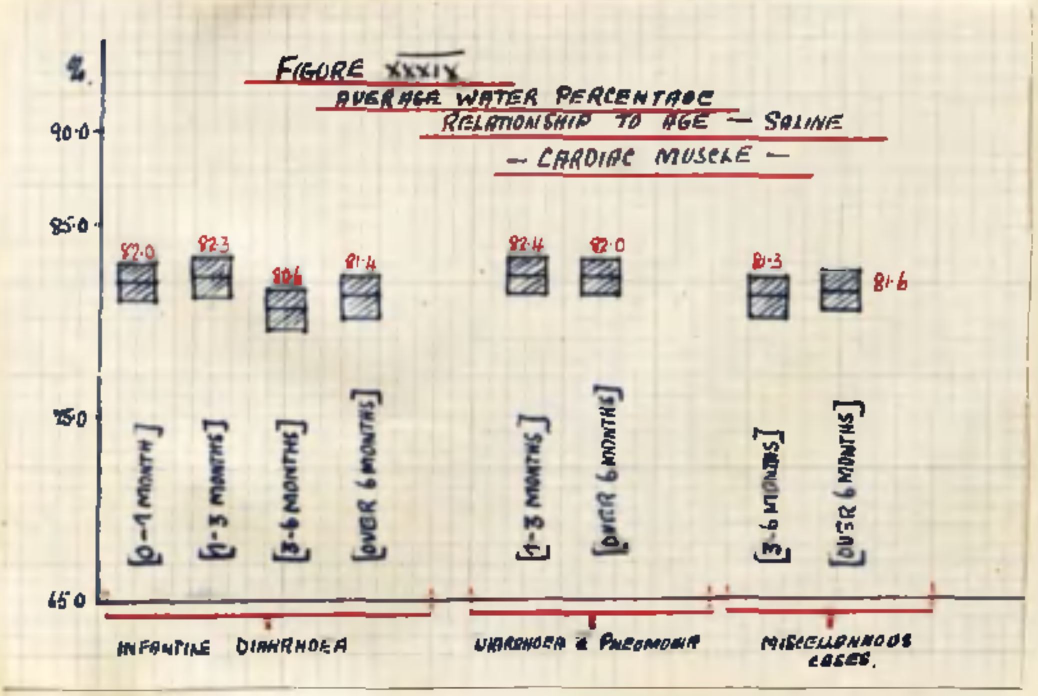


FIGURE XXXIX
AVERAGE WATER PERCENTAGE
RELATIONSHIP TO AGE — SALINE
— CARDIAC MUSCLE —
%.
90·0
85·0
75·0
65·0
82·0
82·3
80·6
81·4
82·4
82·0
81·3
81·6
[0-1 MONTH]
[1-3 MONTHS]
[3-6 MONTHS]
[OVER 6 MONTHS]
[1-3 MONTHS]
[OVER 6 MONTHS]
[3-6 MONTHS]
[OVER 6 MONTHS]
INFANTILE DIARRHOEA
DIARRHOEA & PNEUMONIA
MISCELLANEOUS CASES.

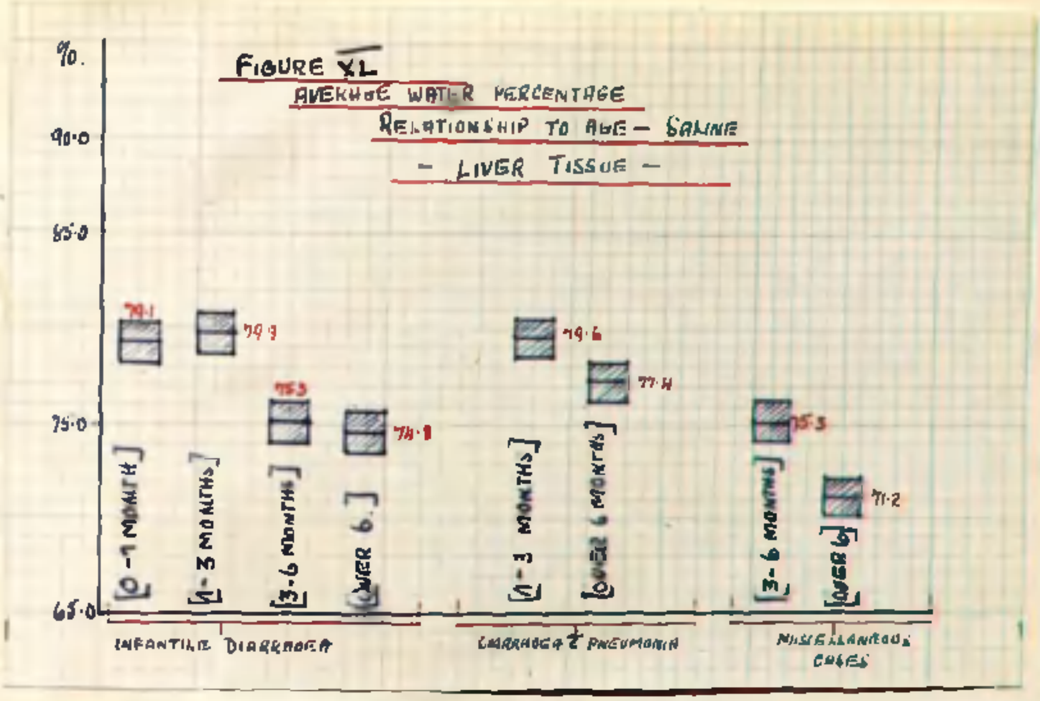


FIGURE XL
AVERAGE WATER PERCENTAGE
RELATIONSHIP TO AGE — SALINE
— LIVER TISSUE —
%.
90·0
85·0
75·0
65·0
79·1
79·3
75·3
74·8
79·6
77·4
75·3
71·2
[0 - 1 MONTH]
[1 - 3 MONTHS]
[3 - 6 MONTHS]
[OVER 6.]
[1 - 3 MONTHS]
[OVER 6 MONTHS]
[3 - 6 MONTHS]
[OVER 6]
INFANTILE DIARRHOEA
DIARRHOEA Č PNEUMONIA
MISCELLANEOUS CASES

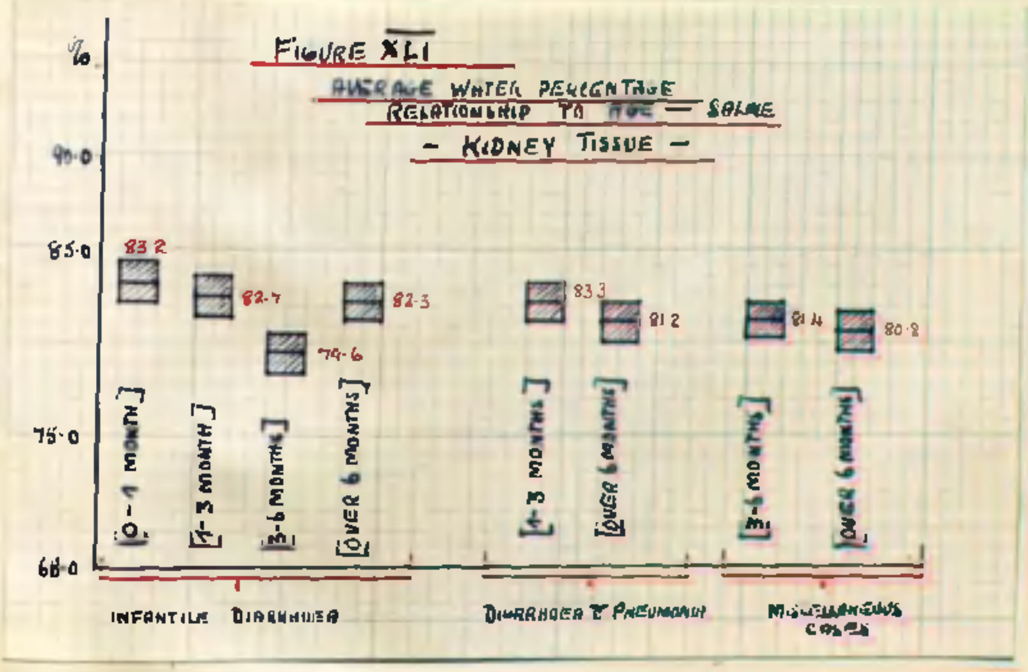


FIGURE XLI
AVERAGE WATER PERCENTAGE
RELATIONSHIP TO AGE — SALINE
— KIDNEY TISSUE —
%
90·0
85·0
75·0
68·0
83·2
82·7
79·6
82·3
83·3
81·2
81·4
80·8
[0 - 1 MONTH]
[1 - 3 MONTH]
[3 - 6 MONTHS]
[OVER 6 MONTHS]
[1 - 3 MONTHS]
[OVER 6 MONTHS]
[3 - 6 MONTHS]
[OVER 6 MONTHS]
INFANTILE DIARRHOEA
DIARRHOEA Č PNEUMONIA
MISCELLANEOUS CASES

(C). Relationship of Chloride and Water Content to Duration of Illness.

It was considered advisable to examine the chloride and water content of the tissues in relationship to the duration of illness, particularly in patients with infantile diarrhoea and vomiting, in whom large amounts of water and salt are lost by the bowel and the vomitus.

The patients in each group were divided into three main categories, thus :-

(a) Duration of illness 0 - 3 days

(b) " " " 3 - 7 days

(c) " " " over 7 days.

TABLE CII.

Chloride Content - Duration of Illness: Miscellaneous Group.

in c.cs. $\frac{N}{10}$ Cl.

Duration	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
0-3 days	37.5	43.9	43.7	49.3	53.9	60.0	6
3-7 "	53.0	44.3	44.2	46.6	46.4	53.8	1
over 7 "	35.6	35.9	42.7	46.0	51.6	64.6	5

As expected, in the tissues of patients belonging to the miscellaneous control group (Table CII), no relationship between the duration of the illness and the average chloride content of the various tissues exists.

In the group suffering from infantile diarrhoea with broncho-pneumonia, all the patients had been ill for a period of more than seven days and are therefore not tabulated.

The group of infantile diarrhoea patients, however, exhibited variable readings for many of the tissues, whether the illness was short or long, although a lowering of chloride did occur in the liver, lung and heart of the patient with the longest history (Table CIII).

TABLE CIII.

Chloride Content - Duration of Illness: Diarrhoea.

in c.cs. $\frac{N}{10}$ Cl.

Duration	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
0-3 days	31.4	46.1	38.3	40.7	48.1	60.7	2
3-7 "	-	-	-	-	-	-	-
over 7 "	45.0	27.5	36.0	40.0	59.3	51.0	1

In the tissues of patients suffering and dying from miscellaneous causes no relationship between the duration of the illness and the water content exists (Table CIV).

TABLE CIV.

Water Content - Duration of Illness:
Miscellaneous Group.

as percentage.

Duration	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
0-3 days	77.6	76.6	81.7	79.5	89.5	80.7	6
3-7 "	77.2	79.8	82.0	81.8	87.6	84.0	1
over 7 "	74.4	76.0	80.6	81.9	84.7	80.6	5

TABLE CV.

Water Content - Duration of Illness: Diarrhoea.

as percentage.

Duration	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
0-3 days	77.6	75.4	81.9	80.3	87.2	82.4	2
3-7 "	-	-	-	-	-	-	-
over 7 "	70.0	70.4	77.0	79.6	84.9	76.2	1

In the group of patients suffering from infantile diarrhoea, the percentage water content of the tissues was lower in that case with the longest history. This is a finding which was expected, and should be considered significant even although the number of cases in this group is small (Table CV).

Saline administration. As the result of saline administration before death, the miscellaneous group showed no evidence that the tissues in short illnesses have the power of fixing larger or smaller amounts of chloride than in those of longer duration (Table CVI).

TABLE CVI.

Chloride Content - Duration of Illness: Miscellaneous Group.

in c.cs. $\frac{N}{10}$ Cl.

Duration	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
0-3 days	-	-	-	-	-	-	-
3-7 "	56.4	34.3	-	49.1	39.1	58.8	1
over 7 "	50.2	40.1	38.1	47.0	47.1	61.8	3

TABLE CVII.

Chloride Content - Duration of Illness: Diarrhoea.

in c.cs. $\frac{N}{10}$ Cl.

Duration	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
0-3 days	67.3	74.0	61.5	71.5	75.0	70.2	1
3-7 "	63.2	58.7	50.0	63.2	55.6	67.1	4
over 7 "	61.4	55.3	54.4	61.3	60.7	71.0	8

In patients dying from infantile diarrhoea, the tissues of lung, heart and brain showed variable values, but the chloride content of heart and brain was highest in the most acute cases. The tissues of liver, kidney and muscle demonstrate that the more acute the illness the greater the power exerted on the fixation of chloride (Table CVII, Figs. XLII and XLIII).

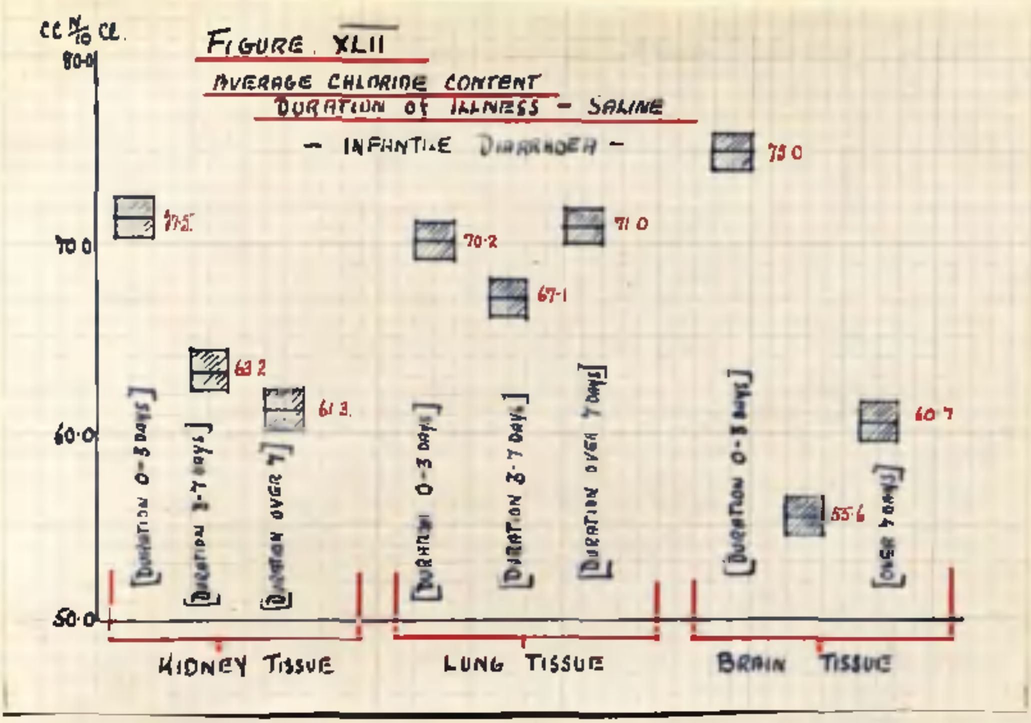
TABLE CVIII.

Water Content - Duration of Illness: Miscellaneous Group.

as percentage.

Duration	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
0-3 days	-	-	-	-	-	-	-
3-7 "	71.8	71.0	-	81.6	87.8	80.1	1
over 7 "	80.0	75.7	83.1	82.3	86.2	84.3	3

The miscellaneous control group, consisting of four patients, did not include any very acute cases (Table CVIII). The water content of the tissues, after saline injection, appeared to be slightly higher, for all except brain, in those infants with longer histories of illness.


cc N/10 Cl.
FIGURE XLII
AVERAGE CHLORIDE CONTENT
DURATION OF ILLNESS - SALINE
- INFANTILE DIARRHOEA -
80·0
70·0
60·0
50·0
71·5
63·2
61·3
70·2
67·1
71·0
75·0
55·6
60·7
[DURATION 0-3 DAYS]
[DURATION 3-7 DAYS]
[DURATION OVER 7]
[DURATION 0-3 DAYS]
[DURATION 3-7 DAYS]
[DURATION OVER 7 DAYS]
[DURATION 0-3 DAYS]
[OVER 7 DAYS]
KIDNEY TISSUE
LUNG TISSUE
BRAIN TISSUE

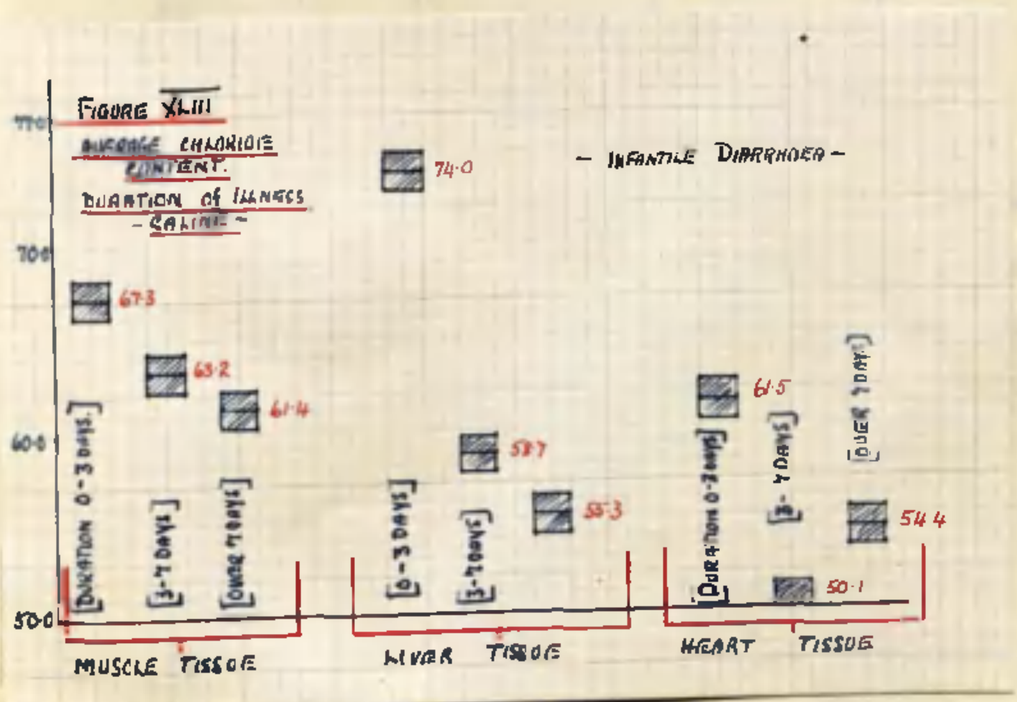


FIGURE XLIII
AVERAGE CHLORIDE CONTENT.
DURATION OF ILLNESS
- SALINE -
- INFANTILE DIARRHOEA -
70·0
60·0
50·0
67·3
63·2
61·4
74·0
59·7
55·3
61·5
50·1
54·4
[DURATION 0-3 DAYS]
[3-7 DAYS]
[OVER 7 DAYS]
[0-3 DAYS]
[3-7 DAYS]
[DURATION 0-3 DAYS]
[3-7 DAYS]
[OVER 7 DAYS]
MUSCLE TISSUE
LIVER TISSUE
HEART TISSUE

In the more acutely ill patients, dying from infantile diarrhoea and treated by saline injections before death, an increase in the water content of muscle tissue only occurred. All other tissue values were rather closely related (Table CIX).

TABLE CIX.

Water Content - Duration of Illness: Diarrhoea.

as percentage.

Duration	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
0-3 days	82.2	78.9	81.4	82.2	88.1	82.4	1
3-7 "	80.1	78.9	81.6	81.8	88.0	80.0	4
over 7 "	78.6	76.4	81.3	81.6	87.2	80.2	8

From these results it would appear that, with or without saline injections before death, no relationship exists between the tissue water and duration of the disease, except in sub-acute diarrhoea where the water content is reduced. Further, in the liver, kidney and muscle of infantile diarrhoea patients fixation of chloride diminishes as the length of illness increases.

(D). Relationship of Tissue Chloride and Water Content to Terminal Temperature.

It would be natural to expect, as the result of fever, a diminution of the body chloride and water since both play an important part in the dissipation of heat. With this in mind, the variations of the tissue chloride and water content in febrile states were examined in the present series of cases. Owing to the fact that the degree of fever varied in each case during hospital sojourn, the only practical method was to correlate the tissue estimations and the terminal temperatures.

The patients in each group were divided into four classes:-

(a) Subnormal temperature

(b) 99-100.9°F.

(c) 101-102.9°F.

(d) 103-106°F. or over.

TABLE CX.

Chloride Content - Terminal Temperature: Miscellaneous Group.

In c.cs.N/10 Cl.

Term. Temp.	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
Subnormal	41.4	43.4	41.8	43.6	59.3	61.1	3
99-100.9°F	31.0	36.5	39.4	43.3	51.8	47.5	2
101-102.9°F	-	-	-	-	-	-	-
103-108°F.	36.9	37.6	42.0	48.4	48.7	64.5	6 *

* All cases of meningitis.

In patients of the miscellaneous control group, the values for the tissue chloride fluctuate widely (Table CX), but the tissues of muscle, liver and brain show the greatest chloride content in cases with a terminal subnormal temperature. The effect of high fever on the chloride values of the tissues does not appear to be noteworthy. In the infantile diarrhoea group, comprising only three cases, the average chloride for all tissues except muscle and brain, showed the highest values in a child who died with a subnormal temperature. Contrary to expectation the lowest values for the average chloride content were not shown by the tissues of a case with high fever (Table CXI).

TABLE CXI.

Chloride Content - Terminal Temperature: Diarrhoea.

in c.cs.N/10 Cl.

Term. Temp.	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
Subnormal	42.4	54.8	44.2	48.1	50.0	64.0	1
99-100.9°F.	-	-	-	-	-	-	-
101-102.9°F.	45.0	27.5	36.0	40.0	59.3	51.0	1
103-108°F.	20.4	37.4	32.4	33.5	46.3	57.5	1

Rather inconclusive figures were shown by the tissues of the infantile diarrhoea with broncho-pneumonia and the broncho-pneumonia groups, but here also the tendency for chloride values to be greater in association with the lower temperatures was found (Tables CXII and CXIII).

TABLE CXII.

Chloride Content - Terminal Temperature: Diarrhoea with Pneumonia.

In c.cs.N/10 Cl.

Term. Temp.	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
Subnormal	-	-	-	-	-	-	-
99-100.9°F.	39.2	59.1	47.5	60.5	-	65.2	1
101-102.9°F.	35.2	45.8	38.6	44.8	-	60.7	1
103-108°F.	37.0	36.9	41.2	45.5	45.8	56.7	2

TABLE CXIII.

Chloride Content - Terminal Temperature: Pneumonia.

In c.cs.N/10 Cl.

Term. Temp.	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
Subnormal	52.5	48.3	42.8	51.1	55.6	67.5	1
99-100.9°F.	-	-	-	-	-	-	-
101-102.9°F.	40.8	40.8	47.2	57.1	-	68.1	1
103-108°F.	42.4	43.1	44.4	47.6	40.1	68.0	6

TABLE CXIV.

Water Content - Terminal Temperature: Diarrhoea.

as percentage

Term. Temp.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
Subnormal	80.8	77.7	82.5	85.3	90.2	81.2	1
99-100.9°F.	-	-	-	-	-	-	-
101-102.9°F.	70.0	70.4	77.0	79.6	84.9	76.2	1
103-108°F.	74.5	73.2	81.4	75.4	84.2	83.7	1

When the percentage water content was studied, in the infantile diarrhoea and broncho-pneumonia groups, higher values were generally found in the tissues of patients with subnormal temperatures. The converse, however, did not necessarily follow (Tables CXIV and CXV).

TABLE CXV.

Water Content - Terminal Temperature: Pneumonia.

as percentage

Term. Temp.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
Subnormal	80.0	79.5	83.7	84.8	87.5	84.1	1
99-100.9°F.	-	-	-	-	-	-	-
101-102.9°F.	75.4	78.0	80.6	81.7	-	84.7	1
103-108°F.	73.1	74.3	79.1	81.1	84.9	81.3	6

In the case of patients dying from infantile diarrhoea with broncho-pneumonia and in the miscellaneous control cases, no relationship between the percentage water content of the tissues and the terminal temperature was observed. The tissue readings showed frequent and marked inconsistencies in each of the thermal groupings (Tables CXVI and CXVII).

TABLE CXVI.

Water Content - Terminal Temperature: Miscellaneous Group.

as percentage.

Term. Temp.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
Subnormal	78.3	75.4	81.9	81.0	90.1	78.5	3
99-100.9°F.	79.2	76.7	81.3	77.0	89.0	80.2	2
101-102.9°F.	-	-	-	-	-	-	-
103-108°F.	74.7	77.7	81.3	82.7	85.5	82.8	6

TABLE CXVII.

Water Content - Terminal Temperature: Diarrhoea with Pneum.

as percentage

Term. Temp.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
Subnormal	-	-	-	-	-	-	-
99-100.9°F.	71.4	75.0	80.0	74.4	-	78.8	1
101-102.9°F.	76.2	78.2	84.1	82.4	-	80.6	1
103-108°F.	75.0	76.7	81.5	81.0	85.4	80.3	2

These results tend to indicate, that no relationship exists between the degree of terminal fever and the chloride and water content of the tissues, with this reservation that, in many tissues, the lower chloride and water values are often associated with fever.

Saline Administration. The sequelae of parenteral saline infusion before death, in relation to the temperature, was next investigated.

In the case of the infantile diarrhoea group, the patients with a terminal subnormal temperature (Table CXVIII), had the greatest chloride content in all tissues except muscle and brain. But again those with the highest degree of fever did not necessarily exhibit the lowest chloride content.

TABLE CXVIII.

Chloride Content - Terminal Temperature: Diarrhoea.

in c.cs.N/10 Cl.

Term. Temp.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
Subnormal	51.7	66.6	58.6	67.6	52.4	72.6	2
99-100.9°F.	67.6	57.5	50.1	61.0	62.4	69.0	6
101-102.9°F.	60.1	56.7	56.0	61.2	61.8	70.2	5
103-108° F.	-	-	-	-	-	-	-

Similarly, in the group of broncho-pneumonia infants, the chloride values of all tissues, except kidney, in the one case which died with a subnormal temperature, were very much higher than the values for similar tissues in febrile cases.

TABLE CXIX.

Chloride Content - Terminal Temperature: Pneumonia.

In c.cs.N/10 Cl.

Term. Temp.	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
Subnormal	77.1	60.0	56.1	50.5	-	71.8	1
99-100.9°F.	-	-	-	-	-	-	-
101-102.9°F.	-	-	-	-	-	-	-
103-108°F.	50.0	46.0	45.5	51.5	50.5	68.1	2

(Table CXIX). No relationship however appears to exist between the chloride content and the degree of fever in the small group of patients dying from infantile diarrhoea with broncho-pneumonia (Table CXX). Nothing can be deduced from the behaviour of the tissues of the miscellaneous control group as there was high fever in all.

TABLE CXX.

Chloride Content - Terminal Temperature: Diarrhoea with Pneum.

In c.cs.N/10 Cl.

Term. Temp.	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
Subnormal	-	-	-	-	-	-	-
99-100.9°F.	57.5	48.6	42.3	47.4	49.4	55.5	2
101-102.9°F.	73.7	62.0	45.1	61.8	55.3	71.0	1
103-108°F.	-	-	-	-	-	-	-

It can, therefore, be accepted that the degree of terminal fever does not directly affect the tissue chloride values of infants whether they have received saline injections or not, although it must be admitted that those cases with a subnormal terminal temperature, do exhibit some greater tissue chloride values than similar cases with varying degrees of fever.

As regards tissue water content after saline administration, infantile diarrhoea patients (subnormal temperature) showed an increase in lung, kidney and muscle. This steadily decreased as the terminal temperature increased (Table CXXI). The tissues of liver, heart and brain, however, showed only slight alterations except in those cases with the highest

TABLE CXXI.

Water Content - Terminal Temperature: Diarrhoea.

as percentage

Term. Temp.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
Subnormal	81.2	77.8	81.5	83.3	87.4	83.7	2
99-100.9°F.	80.8	78.7	82.4	82.6	87.7	80.7	6
101-102.9°F.	76.3	76.4	80.8	81.0	87.2	79.9	5
103-108°F.	-	-	-	-	-	-	-

terminal temperature where the lowest percentage of all was found.

TABLE CXXII.

Water Content - Terminal Temperature; Pneumonia.

as percentage

Term. Temp.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
Subnormal	72.2	73.8	80.3	79.7	-	80.0	1
99-100.9°F.	-	-	-	-	-	-	-
101-102.9°F.	-	-	-	-	-	-	-
103-108°F.	72.8	76.6	81.1	81.4	-	81.4	2

TABLE CXXIII.

Water Content - Terminal Temperature: Diarrhoea with Pneumonia.

as percentage.

Term. Temp.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
Subnormal	-	-	-	-	-	-	-
99-100.9°F.	78.0	77.4	81.6	81.1	86.4	80.4	2
101-102.9°F.	80.3	79.6	82.4	83.3	88.1	82.3	1
103-108°F.	-	-	-	-	-	-	-

The small group of cases suffering from infantile diarrhoea with broncho-pneumonia and from broncho-pneumonia had rather variable results, which however cannot be seriously considered owing to the paucity of numbers in each group (Tables CXXII and CXXIII).

(E). <u>Relationship of Tissue Chloride and Water Content to Percentage Expected Weight</u>.

The percentage of expected weight was calculated by taking into account the relationship between the average weight of the infant for its age and the actual weight, and thus serves as an index for the degree of malnutrition. It was thought that there might be some connection between the chloride and water contents of the tissues and the percentage of expected weight, in that the chloride and water content should be lower in those patients with the most marked malnutrition, i.e. with the lower percentages of expected weight.

For this purpose the patients of each group have been sub-divided into :-

(a) under 50% of expected weight

(b) 50-70% " " "

(c) 70-100% " " "

In the small group of patients dying as the result of infantile diarrhoea, one case was discovered to be under 50% of its expected weight and in this, the tissue chloride exhibited the highest readings in all tissues except brain (Table CXXIV). This was a remarkable and unexpected finding.

TABLE CXXIV.

Chloride Content - % Expected Wt.: Diarrhoea.

in c.cs. $\frac{N}{10}$ Cl.

% Exp. Wt.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
Under 50	42.4	54.8	44.2	46.1	50.0	64.0	1
50 - 70	-	-	-	-	-	-	-
70 - 100	32.7	32.4	34.2	36.7	52.8	54.2	2

In the larger miscellaneous group of control cases, the degree of wasting was not so marked as in the previous group, for the weight of all cases was between 70 and 100% of average (Table CXXV).

TABLE CXXV.

Chloride Content - % Expected Wt.: Miscellaneous Group.

in c.cs. $\frac{N}{10}$ Cl.

% Exp. Wt.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
70 - 80	35.7	40.4	44.6	46.8	50.4	72.6	2
80 - 90	34.5	35.4	36.6	49.1	51.1	57.9	2
90 - 100	42.0	45.1	38.1	48.2	54.7	56.1	2

The tissue chloride values in these cases show marked and conflicting variations with no relationship to the expected weight.

TABLE CXXVI.

Chloride Content - % Expected Wt.: Diarrhoea with Pneumonia.

in c.cs. $\frac{N}{10}$ Cl.

% Exp. Wt.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
Under 50	-	-	-	-	-	-	-
50 - 70	40.9	47.4	42.3	50.6	43.2	60.3	2
70 - 100	33.3	41.9	42.0	47.5	48.4	59.3	2

In patients dying from the effects of infantile diarrhoea with broncho-pneumonia the tissue chloride of liver, muscle, and to a lesser extent those of kidney, showed slightly higher values in the more wasted infants. The older tissue values in this group, however, varied considerably.

TABLE CXXVII.

Chloride Content - % Expected Wt.: Pneumonia.

in c.cs. $\frac{N}{10}$ Cl.

% Exp. Wt.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
Under 50	-	-	-	-	-	-	-
50 - 70	46.7	44.6	45.0	54.1	55.6	67.8	2
70 - 100	39.6	42.8	43.9	50.1	34.9	68.9	5

Rather similar observations were made in patients dying from broncho-pneumonia, the tissue chloride values of kidney, muscle and brain being higher in those cases with the lowest percentage of expected weight (Table CXXVII).

It would thus appear that there is a tendency on the part of some tissues, in all groups except the controls, to exhibit higher chloride values when the percentage expected weight is under or just above 50%.

TABLE CXXVIII.

Water Content - % Expected Wt.: Diarrhoea.

as percentage.

% Exp. Wt.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
Under 50	80.8	77.7	82.5	85.3	90.2	81.2	1
50 - 70	-	-	-	-	-	-	-
70 - 100	72.2	71.8	79.2	77.5	84.5	79.9	2

A markedly increased water content was noted in all tissues of that case of infantile diarrhoea exhibiting the lowest percentage of expected weight. This increased content, as compared with better nourished cases, amounted to as much as 8% in muscle and kidney and 5.7% in brain tissue (Table CXXVIII).

Similarly all the tissues of the broncho-pneumonia group showed the highest average water content with the lowest percentage of expected weight, while the tissues of liver, muscle, heart and kidney showed a progressive decrease as the nutrition improves (Tables CXXIX and CXXIXa).

TABLE CXXIX.

Water Content - % Expected Wt.: Pneumonia.

as percentage.

% Exp. Wt.	Muscle	Liver	Heart	Kidney	Brain	Lung	No. Cases
Under 50	-	-	-	-	-	-	-
50 - 70	77.7	78.8	82.1	83.2	87.5	84.4	2
70 - 100	74.7	73.5	79.5	80.5	84.3	81.9	5

TABLE CXXIXa.

50 - 70	77.7	78.8	82.1	83.2	87.5	84.4	2
70 - 80	75.0	74.8	79.7	80.7	84.2	81.7	4
90 - 100	73.5	68.4	78.7	80.3	84.7	82.8	1

On the other hand the tissues of patients dying as the result of infantile diarrhoea with broncho-pneumonia and miscellaneous causes, showed no relationship between the average water content and the degree of malnutrition, but it should be noted that the state of nutrition in the latter group of infants was fairly good (Tables CXXX and CXXXI).

TABLE CXXX.

Water Content - % Expected Wt.: Diarrhoea with Pneum.

as percentage.

% Exp. Wt.	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
under 50	-	-	-	-	-	-	-
50 - 70	73.9	76.8	81.3	78.2	85.9	80.3	2
70 - 100	74.9	76.5	82.3	81.2	85.0	79.7	2

TABLE CXXXI.

Water Content - % Expected Wt.: Miscellaneous Group.

as percentage

% Exp. Wt.	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
70 - 80	73.6	76.4	81.4	81.2	85.6	81.4	2
80 - 90	75.9	76.3	79.7	79.4	86.0	78.6	2
90 -100	78.9	78.9	83.0	82.2	87.6	81.2	2

It thus remains rather uncertain whether the results in the case of the infantile diarrhoea and broncho-pneumonia groups are significant, but the fact that these patients do show greater degrees of malnutrition than those in the larger miscellaneous group, deserves some consideration.

Saline Administration. On an examination of the results set down for the infantile diarrhoea group which received saline (Table CXXXII), it will be seen that the greatest chloride values were present in all the tissues, except heart, of the most ill-nourished child.

TABLE CXXXII.

Chloride Content - % Expected Wt.: Diarrhoea.

In c.cs.N/10 Cl.

% Exp. Wt.	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
under 50	66.0	66.1	52.7	71.4	-	76.1	1
50 - 70	65.6	59.2	53.4	61.8	64.2	71.1	8
70 -100	54.6	55.3	54.4	60.3	54.1	65.3	4

In those patients who were better nourished, the chloride content steadily and progressively fell until the lowest tissue value was found in cases with an expected weight of 70-100%.

TABLE CXXXIII.

Chloride Content - % Expected Wt.: Diarrhoea with Pneum.

In c.cs.N/10 Cl.

% Exp. Wt.	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
under 50	73.7	62.0	45.1	61.8	55.3	71.0	1
50 - 70	57.7	48.6	42.3	47.4	49.4	55.5	2
70 -100	-	-	-	-	-	-	-

Similar observations to those of the infantile diarrhoea group, were made on the tissues of patients dying as the result of infantile diarrhoea with broncho-pneumonia (Table CXXXIII).

TABLE CXXXIV.

Chloride Content - % Expected Wt.: Pneumonia.

In c.cs.N/10 Cl.

% Exp. Wt.	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
under 50	77.1	60.0	56.1	50.5	-	71.8	1
50 - 70	53.9	55.6	39.8	51.0	50.5	63.6	1
70 -100	46.4	36.4	51.2	52.0	-	72.7	1

The chloride figures in the worst nourished child were the highest for all tissues except lung and kidney in the broncho-pneumonia group (Table CXXXIV) while analysis of the miscellaneous control group failed to show any particular trend of variation (Table CXXXV).

TABLE CXXXV.

Chloride Content - % Expected Wt.: Miscellaneous Group.

In c.cs.N/10 Cl.

% Exp. Wt.	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
under 50	62.1	37.6	40.3	46.3	-	58.4	1
50 - 70	-	-	-	-	-	-	-
70 - 100	48.3	39.0	37.0	47.9	43.1	61.9	3

Examination of Table CXXXVI shows that, in infantile diarrhoea, those patients with the lowest percentage expected weight exhibited the highest water content for all tissues. Muscle shows this alteration particularly well - a variation of no less than 5% (which is large for water content) between the worst and best-nourished children (Fig. XLIV).

TABLE CXXXVI.

Water Content - % Expected Wt.: Diarrhoea.

as percentage.

% Exp. Wt.	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
under 50	82.0	80.0	83.8	84.3	-	86.3	1
50 - 70	79.6	78.6	82.0	82.3	87.9	80.9	8
70 -100	76.9	74.4	80.0	80.9	86.7	79.4	4

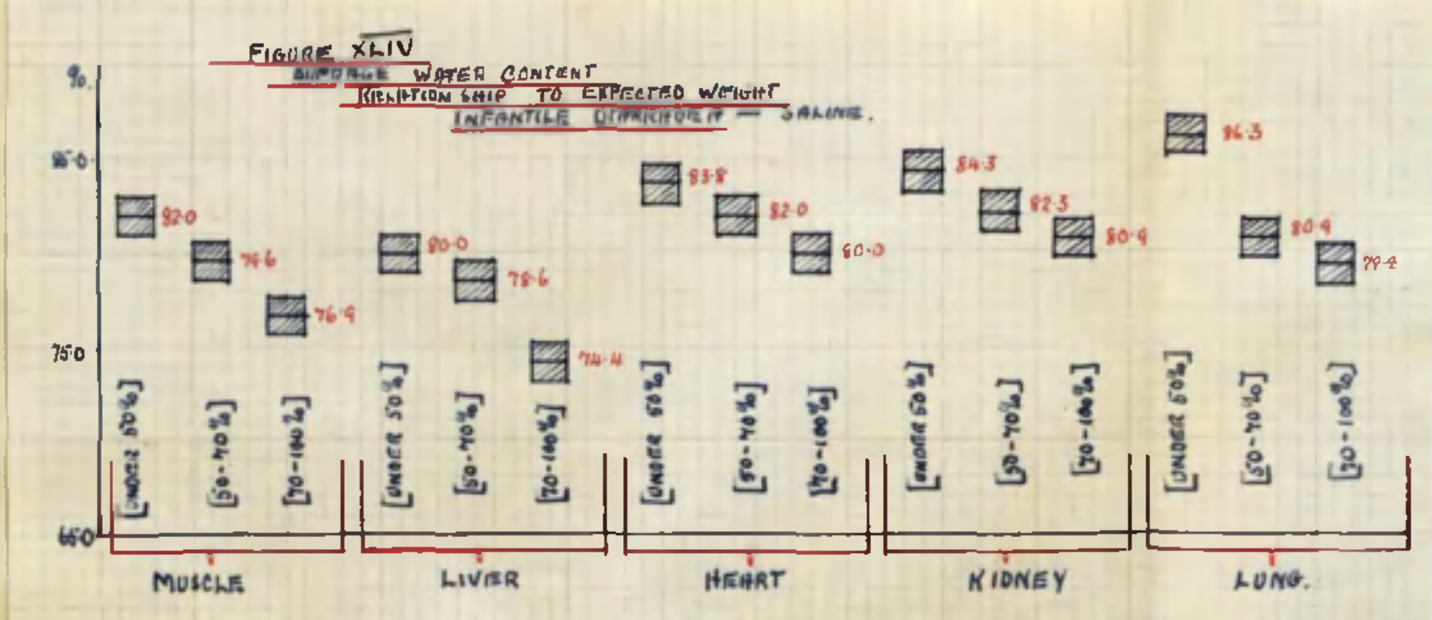


TABLE CXXXVII.

Water Content - % Expected Wt.: Diarrhoea with Pneum.

as percentage.

% Exp. Wt.	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
under 50	80.3	79.6	82.4	83.3	88.1	82.3	1
50 - 70	78.0	77.5	82.0	81.1	86.5	80.4	2
70 -100	-	-	-	-	-	-	-

Similar to those in the infantile diarrhoea group, were the observations made on the diarrhoea with broncho-pneumonia and control groups (Tables CXXXVII and CXXXVIII, Figs.XLV-XLVII), but cases of broncho-pneumonia alone did not

TABLE CXXXVIII.

Water Content - % Expected Wt.: Miscellaneous.

as percentage.

% Exp. Wt.	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
under 50	89.2	80.5	86.4	85.7	-	85.8	1
50 - 70	-	-	-	-	-	-	-
70 -100	74.2	72.5	81.4	80.6	87.0	82.4	3

show any comparable relationship between the average tissue water content and the percentage expected weight (Table CXXXIX).

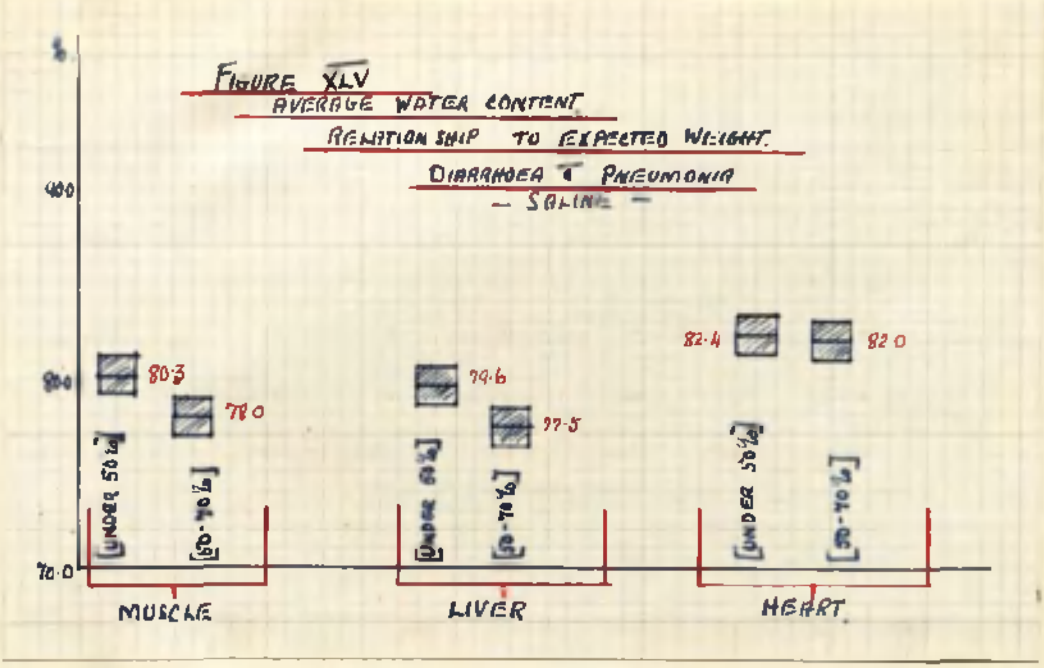


FIGURE XLV
AVERAGE WATER CONTENT
RELATIONSHIP TO EXPECTED WEIGHT
DIARRHOEA ē PNEUMONIA
— SALINE —
%
90.0
80.0
70.0
80.3
78.0
79.6
77.5
82.4
82.0
[UNDER 50%]
[50-70%]
MUSCLE
LIVER
HEART

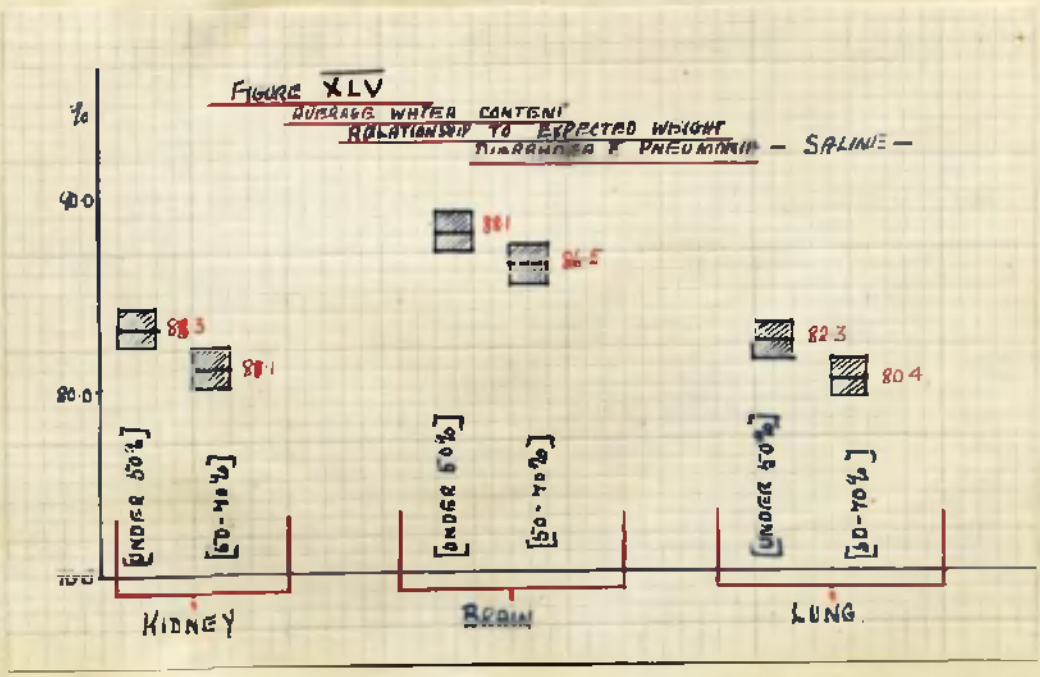
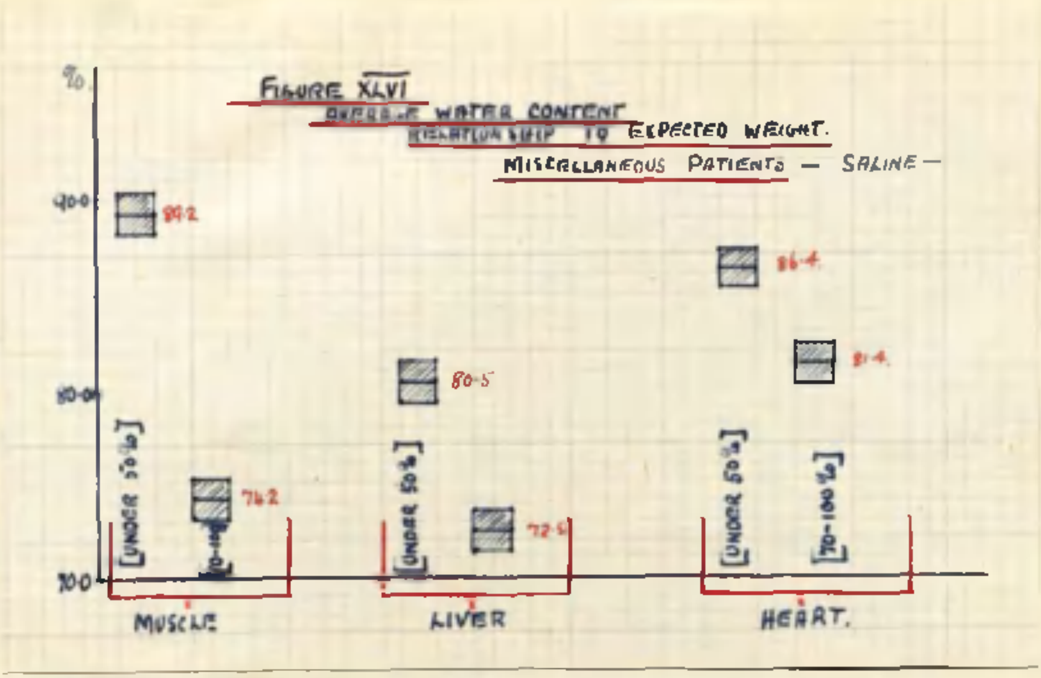


FIGURE XLV
AVERAGE WATER CONTENT
RELATIONSHIP TO EXPECTED WEIGHT
DIARRHOEA ē PNEUMONIA — SALINE —
%
90.0
80.0
82.3
80.4
[UNDER 50%]
[50-70%]
KIDNEY
BRAIN
LUNG


%
FIGURE XLVI
WATER CONTENT
TO EXPECTED WEIGHT.
MISCELLANEOUS PATIENTS — SALINE —
90·0
80·0
70·0
80·5
UNDER 50%
UNDER 50%
UNDER 50%
70-100%
MUSCLE
LIVER
HEART.

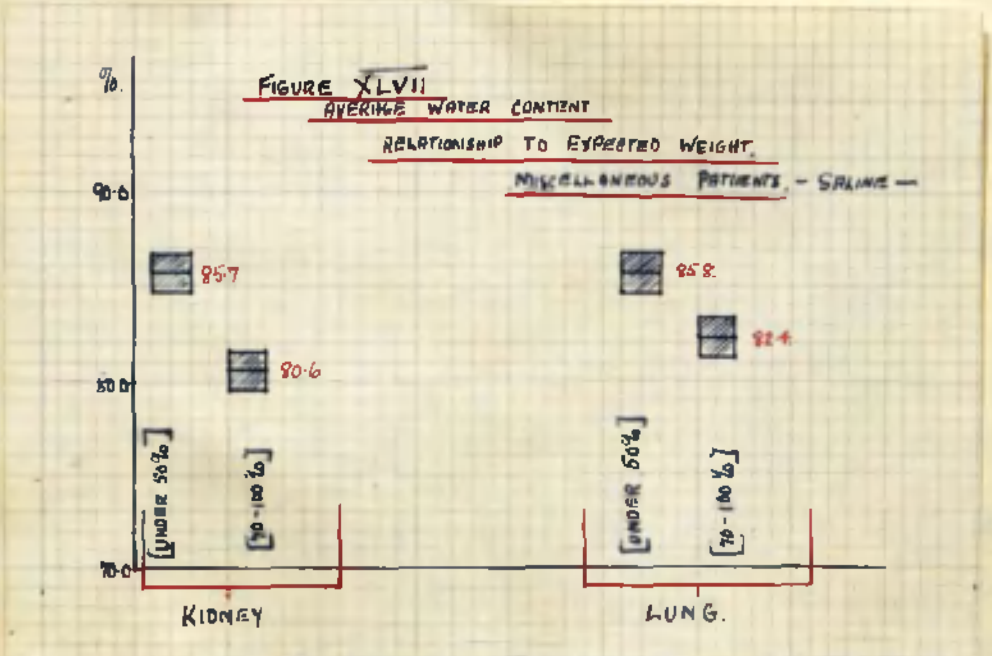

%.
FIGURE XLVII
AVERAGE WATER CONTENT
RELATIONSHIP TO EXPECTED WEIGHT.
MISCELLANEOUS PATIENTS - SALINE -
90·0
80·0
70·0
85·7
80·6
85·8
UNDER 50%
70-100%
UNDER 50%
70-100%
KIDNEY
LUNG.

TABLE CXXXIX.

Water Content - % Expected Wt.: Pneumonia; Saline administered.

as percentage

% Exp. Wt.	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
under 50	72.2	73.8	80.3	79.7	-	80.0	1
50 - 70	71.3	78.6	80.0	80.4	-	82.4	1
70 -100	74.3	74.6	82.3	82.4	-	80.5	1

It would thus appear that a very much greater value for both tissue chloride and water is found in most of those patients, with the lowest percentage of expected weight, as the result of saline injections during life. Whether or not an increased retention of these two substances occurs, is difficult to determine, but the greater average variations, between cases badly and those less severely undernourished, seen in most tissues of cases receiving saline, rather suggests a greater retention in those patients under or near 50% of their expected weight.

(F). Relationship of the Tissue Chloride and Water Content to the amount of Fluid injected.

It was considered quite probable that the amount of fluid administered during life to these patients, would affect both the chloride and the water content of the various tissues.

Taking into consideration the fact that patients suffering from infantile diarrhoea and vomiting comprise the only large group receiving saline, it was decided to employ only these cases in this investigation.

The patients were classified according to the number of intra-venous and intra-peritoneal injections received and the number of days over which these were spread. It should however be mentioned that this sub-division is purely arbitrary, for these patients could not possibly be standardised in respect to the total quantity given, the periodicity of administration, or the severity of their dehydration. It is apparent that the effect of saline on the chloride and water content of patients receiving it one day before death, may be quite different from that seen when twice the volume has been given two days before death etc.. In the classification adopted, however, both types of case cannot be provided for, but no better method for the standardisation of all factors could be devised.

The patients have been sub-divided as follows:-

(a) One saline in 12 hrs. (average)

(b) One saline in 24 hrs. "

(c) One saline in 48 hrs. "

(d) One saline in 72 hrs. "

As was indicated earlier, each injection was of 20-25 c.cs. per kilo body weight. The actual quantities may therefore be ignored, being strictly comparable, irrespective of age and weight.

TABLE CXL.

Chloride Content - Amount of Fluid Injected.

In c.cs.N/10 Cl.

Sub-Group	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
(a)	59.8	73.1	64.8	72.4	61.3	70.2	2
(b)	63.6	52.1	50.7	59.4	58.9	72.5	5
(c)	61.8	64.9	59.9	66.6	67.8	76.7	3
(d)	62.0	48.6	41.3	51.4	55.5	59.7	2

TABLE CXLI.

Water Content - Amount of Fluid Injected

as percentage

Sub-Group	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
(a)	80.2	78.9	80.7	82.7	86.8	83.3	2
(b)	77.3	76.3	81.2	80.7	86.6	79.2	5
(c)	78.7	78.8	82.2	82.3	88.3	83.1	3
(d)	80.7	77.0	82.3	82.4	88.4	79.8	2

On examination of the results, Table CXL, it is not very surprising to find that the tissue chloride values did not vary directly with the different amounts of saline injected, but showed higher contents in some cases who had received less saline than in others who had received more. Similar unpredictable variations of the average water content were also found in these patients (Table CXLI).

(G). Average Tissue Chloride and Water Content - Infections and Non-Infections.

Blacklock and Morris (85) have demonstrated that, when abundant chloride is administered to rabbits suffering from acute and chronic infections, an increased retention of chloride occurs only in some tissues of those suffering from the acute infections. In view of this finding, and in an attempt to discover whether any such relationship held in infancy, the patients in the present series were divided into infections and non-infections, (a) no saline, (b) saline.

(a) No saline given. The patients falling into this group consist of 31 cases, of which five were non-infections.

From an examination of the results (Table CXLII), there is no evidence of an increased retention of chloride in the tissues of patients with infections, although an increase of lung chloride is noted in these patients*. Possibly the fact that many of the patients in the non-infectious group were very young infants accounted for this finding.

TABLE CXLII.

Tissue Chloride - Infections & Non-Infections : No Saline.
In c.cs.N/10 Cl.

Description	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
Non-Infections	39.4	45.4	45.0	48.3	55.2	57.9	5
Infections	40.4	43.3	42.1	47.3	47.5	63.3	26

*Many cases in this group suffered from broncho-pneumonia.

Rather similar findings were noted in the water content of the tissues of these patients. The average water content of the lung, however, showed an increased content in patients suffering from infections (Table CXLIII), but the fact that many of these patients died as the result of pulmonary mischief must be seriously considered.

TABLE CXLIII.

Infections & Non-Infections - Water Content : No Saline.

as percentage.

Description	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
Non-Infections	77.9	75.9	81.6	79.3	90.1	79.6	5
Infections	74.6	76.1	80.7	81.1	85.9	81.2	26

The values for the other tissues were usually higher in those infants with non-infections. Skeletal muscle and brain showed this particularly well, the average content of these tissues being 3.3% and 4.7% higher respectively in the non-infectious group. Possibly the high content in brain tissue is due to the fact that many of these patients considered as non-infections died as the result of intra-cranial haemorrhage.

(b) Saline given. Twenty seven patients fell into this group, four of whom were "non-infections".

As the result of saline administration, by either the intra-venous or intra-peritoneal route, there followed in the infectious group an increased retention of chloride in all tissues, this retention being most marked in muscle and least in brain (Table CXLIV).

TABLE CXLIV.

Chloride Content - Infections & Non-Infections: Saline.

In c.cs.N/10 Cl.

Description	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases
Non-Infections	46.8	47.6	43.2	52.6	56.4	64.2	4
Infections	61.7	55.3	50.3	58.6	58.5	69.1	23

There also was a similar increased retention of water in all tissues of those patients with infections. This increase was most apparent in the case of liver and least marked in the case of brain (Table CXLV).

The increase in liver tissue is interesting as a similar observation was noted by Blacklock and Morris[85] in rabbits with infections, while Mautner and Pick[111] regard the liver as an important organ for storage of water.

It thus appears that, as the result of saline administration, an increased retention of chloride and water occurs in most tissues of those patients with infections.

TABLE CXLV.

Water Content - Infections and Non-Infections: Saline.
as percentage.

Description	Muscle	Liver	Heart	Kidney	Brain	Lung	No.Cases.
Non-Infections	76.3	74.0	80.6	79.7	86.8	80.3	4
Infections	78.4	76.8	81.8	82.0	87.0	81.4	23

DISCUSSION.

Average Chloride and Water Content. The results, recorded in this section, for the chloride values of the tissues indicate the marked variations which are met with even in similar tissues of infants suffering from the same disease. This variability was also commented upon by Ballif and Gherscovice,[91] in the examination of the chloride content of tissues from 60 adult cases, and would thus tend to indicate that a large number of factors must play a part in the regulation of the chloride content. The chloride and water contents are no doubt also affected by the amount of blood plasma present in each of the respective tissues, but to obviate any fallacy, care was taken that any excess fluid was removed before the tissues were weighed.

The lowest and highest figures for chloride content were found in muscle and lung tissue respectively and are in agreement with those of Wahlgren[108] et alii[90] in the case of adult tissues. It would also appear, by comparison of the average chloride content of tissues in adults, as published by Müller and Quincke,[92] and Mach[62] et alii[91][93] with this series of cases, that in infants a definitely greater chloride content occurs in most tissues. Likewise, greater amounts of water are present in the various tissues of infants, as compared with the average water content of adult tissues published by Levy[90] et alii[93][95]. This finding is in agreement with those of McQuarrie[105] and Schneegans,[112] the latter author noting however, quite large variations in the water content of the same tissues.

Although Levy,[90] Engels[104] et alii[95] have described the highest water content as occurring in the lung tissue of adults and dogs, the tissue in infants exhibiting the greatest water content was found to be the brain. As McQuarrie[105] suggests, this markedly increased water content in the brain of infants, as compared with adults, may explain the relative frequency of convulsions in the former. Skelton,[113] however, maintains that the tissues concerned in the transportion of water exhibit greater average water values than those not so engaged. It is interesting to note that in the present miscellaneous control group the water content of cardiac muscle gave slightly greater values than the lung tissue.

It has been suggested by various observers, Seckel,[114] Mellinghoff[115] et alii,[101] that there may be a chloropaenia in patients with infantile diarrhoea and vomiting, but these figures give no definite indication that this occurs, although the chloride content of most tissues is slightly on the low side when compared with the values of the miscellaneous control group. The chloride values, in this series of infantile diarrhoea patients, are however very much greater than those for similar tissues of infants with pyloric stenosis, published by Morris and Graham.[88] This was a rather surprising finding, for it was confidently expected that a definite and marked lowering of both chloride and water would occur in all tissues, as the result of large losses of water and chloride by the bowel and vomitus, but the presence of a normal or only slightly lowered blood chloride in these patients (Part II) also suggests that the amount of chloride lost from the body is not as great as has been supposed.

Blum et alii[(109)] have demonstrated an increased chloride content in all tissues of a patient with diabetic acidosis, while von Caulaert and others[(116)] found an increased chloride content in the muscle of dogs who had received dilute acid intra-venously. It might therefore be suggested that acidosis, so often present in these infants with diarrhoea and vomiting, may be the cause of the normal tissue chloride content.

It is also worthy of note that patients with peritonitis exhibited low chloride values in several of the tissues, including those of kidney, lung, heart and brain. This might have been expected from the demonstration by Orr and Haden[(117)] of a lowered plasma chloride value in cases of peritonitis.

In infants dying as the result of broncho-pneumonia and of diarrhoea with pneumonia, the chloride values of the tissues were rather variable, but frequently slightly greater than those of the miscellaneous control group. It thus appears that there is a slight increase of tissue chloride, in many tissues of broncho-pneumonia, similar to the recorded findings of Hutchison[(95)] et alii[(94)(96)] in the tissues of adults with primary pneumonia.

The chloride values of tissues of the renal disease group exhibited variable and confusing results, when compared with the miscellaneous group. No deductions can be made from this group.

In a consideration of the average water content of the various tissues in different diseases, there still appears to be a great deal of controversy over water exchange. On the one hand Butler et alii [118] and Wiley and Wiley [55] maintain that the body has the power to shift intra-cellular fluid from one tissue to another, the latter authors basing their views on an increased potassium excretion noted in a man dehydrated as the result of fasting. On the other hand Underhill et alii [119] maintain that the tissues give up only a certain definite amount of water which, if excreted, leads to tissue break-down and death. Miller [120] is in agreement with this view, for he has noticed that the special organs of dogs dying as the result of intestinal obstruction exhibit, in their water content, only slight alterations from similar animals not so affected. He suggests that only the interstitial water and the blood plasma water are lost in the vomitus of these animals. Hamilton and Schwartz [106] also maintain that the water lost in cases of dehydration is extra-cellular in origin, and that the tissues of muscle and skin are the main source of this loss, while Rubin and Kellett [25] found no change in the water content of muscle tissue, in guinea pigs dehydrated by feeding on a dry diet, even although a marked decrease of plasma volume and an increase of serum proteins occurred.

The fact that there was no definite decrease in the water content of the tissues of patients dying from diarrhoea is rather in favour of the view that only interstitial fluid is called upon in severe degrees of water loss. Unfortunately no examinations were carried out on the skin, for this appears (clinically) to be the tissue which is affected in patients suffering from diarrhoea and vomiting. Liver tissue values were, however, on the low side in these patients but possibly this was due to a loss of glycogen, as the result of the vomiting and severe malnutrition.

The average water content of the various tissues of the broncho-pneumonia, and diarrhoea with broncho-pneumonia, groups was very similar to the water content in the control infants. The renal group however exhibited rather high values for water content, but the fact that Blum et alii[(109)] have demonstrated an increased water content, in all tissues of patients suffering from renal lesions, will no doubt explain the values present in this series.

Saline Administration. As the result of saline administration within a period of three days of death, there occurred a very marked increase in chloride content of all tissues of the infantile diarrhoea and peritonitis groups. The other groups, with the exception of the miscellaneous and renal, also showed this increase but to a very much less marked extent.

This definite chloride increase in the infantile diarrhoea group might be due to (a) a chloride vacuum in the fixed tissues, i.e. chloropaenia, (b) a diminution in the power of the kidneys to excrete chloride, owing to negative water balance, or (c) deposit of chloride as the result of tissue damage - Chabanier and Lobo-Onell.[121]

It has been demonstrated, however, that no evidence of a definite chloropaenia exists in these patients with infantile diarrhoea, so that it appears more likely that this increased chloride fixation is due to either a diminished power of chloride excretion by the kidneys, or a deposit of chlorides as the result of tissue damage. If the latter view be correct, it appears rather surprising that while all the tissues of patients dying from infantile diarrhoea are affected, only muscle tissue in the case of the miscellaneous group should exhibit an increased chloride content. It would be expected that in a fatal disease one tissue in the body would suffer as much damage as another and, as a result, an increased fixation of chloride would occur in all tissues. The view that renal dysfunction is the main cause is further strengthened by the fact that an increased blood chloride was demonstrated in many of the acute cases after saline injection, and also by the fact that a definite anuria was present in many of these patients owing to the severe water loss by the bowels and vomitus.

The fact that there is a difference between the chloride content of patients receiving saline within three days of death and those receiving it earlier is very suggestive that renal dysfunction is the main factor in the tissue chloride increase.

This increased chloride content, when it does occur after saline injections in the various groups, appears to be most marked in the case of muscle tissue. Wahlgren(108) has also demonstrated that, as the result of saline administration, the main absolute increase occurs in the tissues of muscle, skin and the intestine. It is also worthy of note that those patients of the diarrhoea with pneumonia group, who received no saline within three days of death, exhibited higher chloride values for muscle tissue than those receiving no saline. This finding suggests that, not only is muscle an important tissue for storage of chloride, but it becomes more difficult to reduce its chloride content once this has been raised as the result of saline administration. Similar marked increases of tissue chloride, following saline injections, have been described by Morris, Graham(88) et alii(101) in the tissues of infants with pyloric stenosis and in rats with intestinal obstruction, but neither of these authors has offered any definite explanation of its production.

As the result of saline administration there was a small but definite increase in the water content of all tissues of the infantile diarrhoea group, this being most marked in the case of muscle. Similar changes were observed in the tissues of patients with diarrhoea and broncho-pneumonia, but in the other groups there were no very significant variations. Engels(104) has demonstrated a greatly increased retention of water in the muscle tissues of dogs, but Schnohr(101) found no alteration in the water content of the tissues of rats after giving saline. The tissue analysis of these patients suffering from infantile diarrhoea is in agreement with that of Engels,[104] for muscle tissue was found in these cases to exhibit the most significant water increase after saline injections. The small increase in the other fixed tissues is rather suggestive of the fact that the injected fluid is held by the interstitial tissue spaces and does not become intra-cellular. Undoubtedly some fluid will be retained in the interstitial spaces owing to the marked retention of chloride, but it has been demonstrated by several workers,[85][107][108] and also in this paper, that a dry retention of chloride can and does take place but the amount of water retained to deal with it will not be very great.

The average tissue water content of the renal group does not support the view that the kidneys are the main agents in the retention of chloride in patients suffering from infantile diarrhoea, but as has been mentioned previously many of these patients were not cases of true nephritis.

Age. The results as set down in this series of cases, indicate that to a certain extent the water and chloride content of the tissues varies inversely with the age of the infant, and in a way confirm the views of McQuarrie.[105] Schneegans,[112] however, maintains that at the age of 5 months the tissues exhibit their greatest water content. His views have not been confirmed in this series of patients.

As the result of saline injections before death, the tissues of the infantile diarrhoea group exhibited a greater capacity for the storage of water and chloride in the younger infants. This increased capacity for the storage of water was, however, not particularly well shown in brain, heart or kidney tissues. The tissues of infants belonging to the other groups showed rather variable results, but these are probably due to the small number of patients in each group.

Duration of Illness. The duration of the illness appears to have no effect on either the water content or chloride value of the tissues of patients dying as the result of broncho-pneumonia or miscellaneous causes. This is a finding which occasions no surprise. In the small infantile diarrhoea group, however, small chloride losses occurred only in liver and lung tissues of those cases with the longer history. Similar losses of water were observed in all tissues of this group. This was expected in these patients with long-continued diarrhoea and vomiting, but the finding of a chloride loss in only two tissues cannot be satisfactorily explained.

As the result of saline injections, the tissues of the infantile diarrhoea group exhibited a marked increase in fixation of chloride, in those patients with the shorter history. The average water content, however, except in muscle tissue, was no higher in those with a short history than in those with a longer history. No significant alterations in the chloride and water content of the miscellaneous group were noted. The increased fixation of chloride, in the tissues of infantile diarrhoea patients with a short history, appears of some importance and is most likely due either to an increased fixation of chloride in the tissues as the result of acidosis and tissue damage, or to diminished renal function, the result of a negative water balance. It is known, however, that a more marked tissue breakdown does occur in these patients (high blood N.P.N). Nevertheless, the fact that many of them suffer from a negative water balance would rather suggest that the consequent renal dysfunction is the main factor in shunting the chloride to the tissues, where it is fixed until such time as the body has had its fluid loss restored.

Terminal Temperature. There was neither diminished nor increased retention of chloride and water, in any of the groups, attributable to terminal fever. This finding is not at all surprising, considering that the terminal temperature is no criterion of the degree of fever exhibited during life. It should be noted however that an increased chloride and water content was present in many of the tissues of patients with a subnormal terminal temperature.

Similarly, as the result of saline administration before death, an increased chloride and water content was found in the tissues of those of the infantile diarrhoea and broncho-pneumonia groups who exhibited a terminal subnormal temperature. This increase is no doubt due to circulatory failure, and appears to be a praiseworthy attempt on the part of the body to shunt excess water and chloride into the tissues, so as to lessen the work of a failing heart. Decreased renal efficiency probably also plays a part in this phenomenon. Adolph and Lepore,[78] however, have demonstrated that with a lowering of the blood pressure the water content of the tissues is diminished. This view is therefore not in agreement with the findings of the above authors.

Percentage Expected Weight. In an examination of infants, especially those of the infantile diarrhoea group, who had lost a great deal of weight, a marked lowering of the water and chloride content of the tissues was expected in those with the lowest percentage of expected weight. This, however, was not found.

In patients of the miscellaneous and broncho-pneumonia groups, no relationship between the chloride and water content of the tissues and the percentage expected weight was shown, but the fact that many of these infants did not exhibit such degrees of wasting as the previous group, will possibly explain this.

Can the tissue values in the infantile diarrhoea group be explained by either a loss of fat or a break-down of tissue cells with the liberation of bound water, the tissue cells themselves being metabolised and removed? It appears rather unlikely that the cells themselves can be metabolised without loss of chloride and water, although the fact that cell shrinkage can take place and with it an increased fixation of chloride owing to tissue damage,[121] must be appreciated. This view however does not explain the increase in the water content of these tissues. An increase of chloride and water in liver tissue of athreptic infants has been described by Frank and Stolte,[122] while Ohlmuller[123] also demonstrated that the water content of the organs of athreptic infants was higher than those of normal infants. Similarly Underhill and Fisk[56] have demonstrated that lean animals yield more water than fat ones.

Miller[120] mentions that fat contains only about 10% of water, so that in patients with severe fat loss a proportionately increased water content will result. It would thus appear that loss of fat is the main factor in the increased chloride and water content in tissues of severely under-nourished patients. It must be realized, however, that the total chloride and water content of these infants is probably not increased, but that the increase is only apparent, not real.

As the result of saline administrations, the chloride of the tissues was higher in those patients with the lowest percentage expected weight, in the infantile diarrhoea, broncho-pneumonia and diarrhoea with pneumonia groups. This finding does not necessarily signify that an increased fixation of chloride occurs, but, taken in conjunction with the values in those receiving no saline, which were also high, it is rather suggestive that the loss of fat is the main factor here also. It should however be appreciated that some part, although probably a small one, is played by renal dysfunction in this tissue chloride increase.

The average water content after injections, was higher in most tissues of the severely under-nourished patients with infantile diarrhoea but rather variable in the broncho-pneumonia group. In diarrhoea with pneumonia, although increases of chloride occurred in the tissues of those severely under-nourished, no increase in the water content was observed. This finding suggests a "dry retention" of chloride and has been fully discussed in previous pages.

Amount of Fluid Administered. In patients suffering from infantile diarrhoea, no relationship exists between the tissue chloride or water content and the average amount of fluid injected. This finding may be due to inability to standardise the various conditions met with in different patients.

Infections and Non-Infections. In those patients suffering from infections no increase in the tissue chloride and average water content was noted, except in lung. The fact that many of the patients in the group of infections (not saline treated) suffered from broncho-pneumonia rather suggests that the lung consolidation was the cause of the increase. These findings are, however, not in agreement with the views of Soule, Buckman and Darrow[70] who state that an increased water content occurs in the blood and the tissues of patients with fever.

In patients to whom saline was administered, an increased retention of both chloride and water occurred in most tissues of those with infections. This increase was more marked for chloride in the tissues of muscle and least in brain, while the increase of water was more marked in liver and least apparent in brain. The fact that many patients with infantile diarrhoea have been included in the group of infections should, however, be realized for, as has been previously demonstrated, the greatest chloride and water increase occurred in the tissues of these patients after saline administration. These findings, therefore, are not as significant as they appear to be at first sight.

Conclusions.

1. The chloride and water content of the tissues of infants is greater than that of adults.

2. No definite loss of chloride or water occurs in the tissues of patients dying from infantile diarrhoea and vomiting.

3. A retention of chloride can occur in the tissues without a similar retention of water.

4. In infantile diarrhoea and peritonitis, as the result of saline administration, there is a very marked fixation of both chloride and water in the tissues. Muscle appears an important tissue in this storage.

5. The chloride and water content of the tissues appears to vary inversely with the age of the infant, especially in infantile diarrhoea. The younger the infant the greater the capacity to fix chloride and water, as the result of saline administration before death.

6. No definite relationship between the chloride and water content with the amount of fluid injected or the terminal temperature is apparent, although those patients with a subnormal temperature exhibit greater chloride and water values after saline, than do those with varying degrees of fever.

7. Patients with the lowest percentage expected weight, often show high percentage chloride and water content and also a greater retention of these substances after saline administration.

8. Increased fixation of chloride in tissues after injections of saline suggests renal insufficiency as the result of a negative water balance.

PART V.

Treatment of Diarrhoea in Infancy.

PART V.

The Treatment of Infantile Diarrhoea.

The importance of infantile diarrhoea, as it is met with amongst the hospital classes in a large industrial city, has been demonstrated in Part I of this paper. It was startling to note that the mortality rate in a series of patients suffering from various degrees of diarrhoea and vomiting amounted to as much as 47.3%. Hartmann (124) et alii (33)(40) have recently demonstrated that the mortality rate can be reduced by improved methods of handling and treatment of these infants.

The high mortality rate is of some importance, if only to impress on the general community that prophylactic measures are vital. The aetiological factors concerned in this condition are legion, but it has been demonstrated in Part I (Table VIII) that 97% of the infants affected, were artificially fed. It would thus appear that breast fed infants are practically immune, and that by breast feeding the incidence of the condition in infants would be greatly diminished. There must no doubt be something at fault in the methods of artificially feeding these infants, for the condition is practically confined to the poor communities of large cities. Better houses and the eradication of slums as well as the rapid growth of welfare centres, where mothers can receive advice on the correct feeding and precautionary methods to be adopted with their children, will, no doubt, in time reduce both the incidence and the mortality rate of this disease to a minimum.

Treatment received by cases in Part I.

It was absolutely impossible to compare the mortality rates with the type of dietetic treatment each patient received, owing to the varying degrees of severity in individual cases, which were treated each according to the symptoms exhibited (Table CXLVI). All the cases admitted to the wards with a history of alimentary disturbance or exhibiting the signs and symptoms of such a condition, were given as a routine both a bowel and stomach lavage, provided they were not too shocked, and nothing was given by mouth for periods varying between six

TABLE CXLVI.

Treatment & Mortality Rate - 300 Patients - Diarrhoea and Vomiting.

Type of Treatment	Number of Cases	% Mortality	Total Number
S.C.M. or B.C.M.	56	19.6%	300 Cases
S.C.M. + Intra-Peritoneal Saline	62	45.1%	
S.C.M. + Intravenous Glucose	34	61.7%	
S.C.M. + anti-gas gangrene serum	3	100%	
S.C.M. + I.P. and I.V. glucose	58	72.4%	
Transfusions and salines	18	77.9%	
W.M. or ½ milk and water only	43	27.9%	
S.C.M. + I.P. + I.V. & bacteriophage	2	-	
Not recorded	24	-	

S.C.M. = Sweet curd mixture. I.P. = Intra-peritoneal.

W.M. = Whole Milk. I.V. = Intra venous.

and twelve hours. The performance of the stomach lavage is very often successful in controlling the severe and repeated vomiting so often present in many of these patients.

<u>Types of Fluid in General Use.</u>

It will be observed that many patients (Table CXLVI) received parenteral injections of fluid, which was administered either by the intra-peritoneal or intra-venous routes. These injections were considered necessary owing to the dehydration and negative water balance present in many of the infants and also to the fact that the main channel for fluid administration is out of action, as the result of the severe and repeated vomiting.

Normal isotonic saline would appear to be the most easily obtainable fluid for administration, but Hartmann[21] et alii[22] [41] have been adamant in forbidding its use owing to the fact that chloride is increased at the expense of the bicarbonate and the acidosis becomes more severe and intense. They have advised the use of Hartmann's buffer lactate solution in all these cases, especially when severe acidosis is present. In several of the patients, (Part II, Table XXVI), an increase of blood chloride did occur after saline and glucose administrations, but whether a decrease of bicarbonate occurred cannot be stated as no estimations on this substance were carried out in this series. The fact that no definite increase in the clinical severity of the acidosis occurred, rather suggests that such an occurrence did not take place. Hoag and Marples[57] are also of the opinion that isotonic saline and glucose solutions are of decided value in the treatment of these patients, but did not observe any evidence of a chloride acidosis in their series of patients so treated. In the series of 300 patients summarised in Part I of this paper, 44 - 22 acute and 22 chronic - received intra-venous or intra-peritoneal injections of Hartmann's solution (Table CXLVII).

TABLE CXLVII.

Patients treated by Hartmann's Solution - Mortality.

Type of Case	Number	% Mortality	Total Mortality	Total Number
Acute Cases	22	63.6%	70.5%	44
Chronic Cases	22	77.2%		

The mortality rate in this series was even higher than the total mortality rate of the whole group and as it was observed that the results obtained were no better than those with glucose and saline, its use was discontinued in the treatment of the later patients of the series. It would thus appear that the labour expended in preparing Hartmann's solution was not compensated for by improved results, and as glucose and saline solutions are easily prepared, these should be employed for intra-venous parenteral administration to infants with alimentary disturbances and water loss. It is essential however that 5% glucose solutions, although reported favourably upon by Grulee and Sanford(125), should not be used for intra-peritoneal injections in dehydrated infants, owing to the marked alterations likely to be produced by this solution on the circulating volume, as is indicated by the experimental results in rabbits (Part III).

Acute Infantile Diarrhoea.

Many of these patients when first seen are severely dehydrated and suffer from varying degrees of shock. The first essential in their treatment is the combating of this shock by means of heat and stimulants, but the main factors appear to be (a) refilling of subcutaneous water depots and (b) the promotion of a satisfactory renal action.

Although it has been demonstrated in Part IV (Table LXXVI) that there was no definite water depletion in the fixed tissues of patients dead from infantile diarrhoea, it must be emphasised that this finding merely indicated that the intra-cellular water was not affected by dehydration and water loss. The subcutaneous and interstitial water depots must be depleted of their normal water content, particularly the skin, for the loss of elasticity of this tissue is due to lack of water in the subcutaneous tissue spaces. It was also demonstrated in Part IV (Table LXXVI) that, as the result of saline and glucose administrations, a slight but definite increase of water content occurred in most of the fixed tissues of these patients. This increase must be due to retention of water in the connective tissue water depots of the various organs, and suggests that fluid is stored in most parts of the body, muscle tissue being of special importance for this purpose.

In many of the patients with acute symptoms, (Part II, Tables XX and XXIII), an increased concentration of the serum proteins and non-protein nitrogen occurred. The increase of the former was shown to be due to diminished plasma water and the latter was suggested as being due to both an increased tissue breakdown and to renal dysfunction, the result of a negative water balance. The effects of repeated saline and glucose injections on these blood constituents are shown in Table XXVI, Part II. In many cases there occurred a fall of both the serum protein and non-protein nitrogen values, as a result of these injections. In two patients however, (cases J.M. and B.O'H.), it was suggested that the increase of both serum proteins and non-protein nitrogen was due to insufficient fluid being administered. It thus appears that in some of these patients, sufficient fluid cannot be administered, even by repeated injections, to institute a positive water balance and promote a satisfactory renal response. Recently Karelitz et alii [33] [40] have demonstrated the continuous intra-venous drip saline and glucose method, by which very large quantities of fluid can be steadily and safely administered over periods varying between

24-28 hours, until the tissues have been rehydrated and a satisfactory renal action promoted. This method would seem to be ideal in cases such as those which have just been described.

Karelitz and Schick[33] and Cohen et alii[40] have demonstrated that the mortality rate has been markedly reduced by the use of this method in very acute and severe cases, (Table II - Part I). It is of interest however to note that Monrad, in 1923, demonstrated a mortality rate of only 21% in his series, but no doubt many of the infants in his group were mild cases.

Increased retention of chloride in the blood, (Part II, Table XXVI), and in the tissues, (Part IV, Table LXXIV), was observed after the saline and glucose injections. This fixation or retention was suggested as being due to a negative water balance, chloride being shunted to the tissues owing to deficiency of water for its removal from the body. It is probable that such a marked increase of tissue chloride will not occur if sufficient fluid is administered, preferably by the continuous intra-venous drip method, to produce a positive water balance and a satisfactory renal function.

As the result of single intra-venous glucose and saline injections, it was demonstrated that a diminished movement of fluid between the circulation and the tissue spaces occurred in patients with acute diarrhoea, (Part II, Tables XXXIII to XXXVIII). This diminished movement is probably due to a lowering of the blood pressure. The estimation of blood pressure is difficult in infants, but nevertheless was successfully carried out in one patient, where it was found to be low (Table XXXIII M.McL.). It was discovered however that the use of calcium gluconate resulted in an increased movement of fluid from the circulation to the tissues and it may be suggested that calcium gluconate should be employed as a routine in all cases of acute infantile diarrhoea which are receiving intra-venous saline or glucose injections. As there is a great likelihood that the blood pressure is lowered in these patients, it is also tentatively suggested that epenephrine should be used, especially after large intra-venous injections. Similar suggestions have been put forward by Powers[126], Karelitz et alii[33].

It has also previously been demonstrated, (Part IV), that the water content of the tissues varies inversely with the age, so that in the younger infant a greater proportionate amount of fluid will probably be necessary to rehydrate the tissues and promote a satisfactory and free renal action. This increased water content in the younger infants, no doubt, partly explains the higher mortality rate occurring in them as the result of alimentary disturbances with severe water loss.

<u>Blood Transfusions</u>. Karelitz[33], Johnston[127] et alii[126] have advised that blood transfusions should be carried out on all infants suffering from acute infantile diarrhoea and vomiting. Marriott[15] however has condemned the use of citrated whole blood transfusions in the acute type of patient, until

the fluid balance has been restored. Transfusions given in the presence of marked blood concentration, may result in still further increases in the plasma protein content and intensification of the anhydraemia. A case in point is one in which the blood values are tabulated, (Part II, Table XXVI, case J.M.), and in which the serum proteins and the non-protein nitrogen values were high when two blood transfusions were carried out. This case terminated fatally. In the three hundred patients suffering from infantile diarrhoea, considered in Part I, 18 received blood transfusions as part of their treatment (Table CXLVIII).

TABLE CXLVIII.

Patients Receiving Blood Transfusions.

Type of Case	Number	% Mortality	Total Mortality	Total Number
Acute cases	3	100%	77.7%	18
Chronic cases	15	73.3%		

Three of this number were acute cases and all of them terminated fatally, while of the 15 chronic cases eleven died. These figures, although small in number, are in agreement with the views expressed by Marriott[15] that transfusions should not be given to patients suffering from the acute type of diarrhoea and vomiting.

Chronic Infantile Diarrhoea.

As has been mentioned previously, infants suffering from chronic infantile diarrhoea are liable at any time to develop acute symptoms which, when they occur, will need energetic and prolonged treatment by means of saline and glucose administrations.

The main consideration however, in many of these patients, is the treatment and improvement of the general nutrition which is so often very poor. In cases where fluid injections are indicated there should be no reluctance in giving intra-venous 10% glucose and saline solutions, for they appear just as able as normal infants to metabolise large amounts of glucose (see Table XLIII A.H.).

Parenteral infections, when recognised, should receive adequate treatment. In all patients of this series, where otitis media was detected, paracentesis of the drums was carried out as a routine. It is impossible, from examination of the case records, to state whether the benefit derived from this procedure was marked but in many cases a fall in temperature was observed.

In certain patients suffering from chronic diarrhoea, saline and glucose injections caused alterations in the serum protein similar to those found in patients with acute gastro-enteritis. Others however showed fluid variations, after these injections, which were similar to those of normal infants. The effect of calcium gluconate on these variations appeared in two patients (Tables LI and LII, Part II) to be of some benefit, as an increased passage of fluid from the circulation into the tissue spaces was found.

Blood Transfusions. A marked improvement in these infants after blood transfusions has been noted by Bakwin[128] et alii[15][129], but Wood and Aden[130] maintain that blood transfusions are not a specific cure for chronic infantile diarrhoea, although in many infants they appear to turn the scale in a favourable direction, when used in conjunction with general treatment. The results of blood transfusion on the chronic cases of this series (Table CXLVIII) have not been very encouraging as eleven died out of fifteen treated in this way.

In the treatment of infantile diarrhoea no hard and fast rules can be made. Each patient must be treated according to the individual manifestations of dehydration and toxicity, and the response obtained to whatever therapeutic measures are instituted. The main consideration however is, in acute gastro-enteritis, the promotion of a satisfactory renal response; in the chronic cases, improvement of the general nutritional state.

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