"THE METABOLISM OF CALCIUM AND PHOSPHORUS IN NEPHRITIS."

———oOo———

INTRODUCTION.

***
*

The observations, reported and discussed, in this thesis, were made in the medical wards and biochemical laboratory of the Royal Hospital for Sick Children, Glasgow. The work owes its inspiration to Professor Leonard Findlay whose continuous interest and helpful criticism the writer has greatly appreciated. Every facility for investigation of cases has been freely granted by Professor Findlay and Dr. G.B.Fleming, and is hereby gratefully acknowledged. The advice of Dr. N. Morris on matters of biochemical analysis has been invaluable, and the writer is further indebted to Dr. Morris and Dr. Macrae for the use of certain figures acknowledged in the text, and to the Directors of the Carnegie Trust for the financial assistance afforded by a Carnegie Research Scholarship.

In view of the fact that the variations in blood calcium and phosphorus in renal disease are very incompletely understood, any further attempt to elucidate their metabolism requires no justification. Previous observations have been confined mainly to the aberrations found in the serum values, but in the present investigation a much more comprehensive study has been made, and the work is presented in various sections. The literature appropriate to each section is detailed prior to consideration of the results of the present enquiry, and the sections are arranged as follows.

1. The serum content of calcium and inorganic phosphorus in nephritis.
2. The utilisation of calcium and phosphorus.
3. Absorption of phosphorus.
4. Absorption of calcium.
5. /

5. Excretion A – Urinary excretion of calcium and phosphorus.
   B – Faecal content of calcium and phosphorus.
   C – The evidence of intestinal excretion of calcium and phosphorus in nephritis.

6. General considerations – acidosis etc.

7. Summary.

The methods of analysis are detailed in Appendix I; the case-histories of the principal subjects of the investigation are supplied in Appendix II.

Since reference to Tables and Charts occurs in different sections of the thesis, these have been grouped for the sake of convenience immediately after the Bibliography.

- - - - - - - -

I.

Calcium and inorganic phosphorus of blood serum in nephritis.

Historical: During the past fourteen years frequent reference has been made to the alterations found in various constituents of the blood in renal disease. Considerable attention has been given to the behaviour of urea, chlorides, creatinine, calcium, phosphorus etc. and it has been shown that the aberrations of many of these substances are intimately associated. Thus Hartmann and Darrow have recently contended that increase in urea content is an attempt to compensate for decrease in serum electrolyte, and should not be regarded as the result of failure of renal excretion. Similarly, decrease in serum calcium has for many years been known to coincide with diminished plasma protein and increased inorganic phosphorus. So close is the relationship of these three that a formula has been elaborated whereby the calcium can be calculated for known values of the other two. The part played, in these blood changes, by the damaged kidney is still obscure and the evidence conflicting. This is especially true with regard to phosphorus.

Previous workers on blood phosphorus in renal disease have been unanimous as to the occurrence of a high serum inorganic phosphorus, the elevation depending on the degree of acidosis. Howland and Marriott (30), Denis and Minot (7), Denis and Hobson (8), Fetter (10), De.Wesselow (9), Salveson and Linder (38) each reported a series of observations, and were agreed that the increase in inorganic phosphorus was due to "retention of phosphate" by the kidney. This conclusion was based on the finding of a low urinary output of phosphorus in nephritis, and seemed to be an adequate explanation of the alteration in serum content until Boyd Courtney and McLachlan, after determining the phosphorus balance, expressed a doubt as to its accuracy. Reference

to/

to the above reports will be made in more detail later on.

In 1927 Byrom and Kay (6) examined the blood phosphorus in detail in a large number of cases of nephritis, and demonstrated that there was no increase in total blood phosphorus but merely a redistribution. This they traced to changes in the red corpuscles, the increase in inorganic phosphorus being greatest in presence of severe anaemia. In normal blood the distribution of the ester phosphorus was found to be:- in the red corpuscles 97%: in the lencocytes and platelets 2%: in the plasma 1%. The changes in nephritis were shown in the chemical classification of blood phosphorus arranged as follows:-

1. Acid soluble Organic (Ester)P. hydrolysable / non-hydrolysable 98% in red cells

   Inorganic P. (= ½ of total blood P.)

2. Alcohol-ether soluble - Lipin P.

3. Residual P. - a very small quantity.

The inorganic phosphorus increased at the expense of some of the non-hydrolysable ester phosphorus, the total acid-soluble phosphorus remaining unchanged.

Papers published within the last two years have continued to refer to "retention of phosphate", using the term as synonymous with "retention of phosphorus". Throughout the entire literature, the two expressions have been used to convey the same idea, but in this paper it is proposed to consider the phosphorus metabolism from the standpoint of a possible phosphorus retention; and to omit the term "phosphate retention" except when citing references.

As regards calcium, many observations have been reported on the low serum level in nephritis. Marriott and Howland, (30) Halverson Mohler and Bergeim, (13) Kramer Tisdall and Howland, (27) Denis and Hobson, (8) De Wesselow, (9) Salveson and Linder (38) among earlier workers and Boyd Courtney and McLachlan, (4) Scriver, and (39) Salvesen/

Salvesen[36] within the past few years, have left no doubt as to its occurrence, but differed considerably in assessing the significance of the decrease. Formerly it was thought that "retention of phosphate" led to excessive excretion of calcium by bowel, thereby causing the decrease in serum level. Boyd Courtney and McLachlan[4] however, showed that the calcium balance was as a rule positive, i.e. that there was a retention of calcium; while Salvesen[36] was of opinion that two causal factors were combined to effect the reduction - (1) decrease in plasma protein, and (2) "phosphate retention".

Further reference to these observations will be made in the section dealing with the calcium and phosphorus balances. At present it will suffice to indicate that the general consensus of opinion has favoured retention of phosphorus and excessive excretion of calcium, and that the one series of balance experiments was not sufficiently conclusive to cause these theories to be abandoned. Further investigation seemed to be called for, and the present series of observations was undertaken primarily with a view to determining the calcium and phosphorus balances in nephritis.

Observations. In pursuit of this end, a number of children suffering from renal disease have been examined during the past year. Consequently there are available a considerable number of estimations of serum calcium and phosphorus, and it is proposed to report these briefly before detailing the results of the investigations into calcium and phosphorus metabolism. Since appreciation of the aberrations found in nephritis depends primarily on the limits accepted as those of physiological variation, the normal standards accepted by other observers are of interest.

Howland and Kramer indicated that the average value for inorganic phosphorus in the serum of healthy children was

5.4 mgs/

5.4 mgs. per 100 ccs., with a range of 4 to 7.1 mgs. Wills stated that the recognised limits for serum inorganic phosphorus in normal children were 3.2 to 6.5 mgs., with an average value of 4.1 mgs. per 100 ccs.. Her own series of observations showed the average value to be 4.8 mgs., with extremes of 4.1 and 6.1 mgs. per 100 ccs. of serum.

	Serum Ca. in mgs. per 100ccs.			Serum P. in mgs. per 100ccs.		
	Average	L.V.	H.V.	Average	L.V.	H.V.
Howland & Kramer	-	10	11	5.4	4	7.1
Wills (a) reported	-	9.5	11.5	4.1	3.2	6.5
(b) own cases	10.4	10.1	11.1	4.8	4.1	6.1
Jones & Nye	10	-	-	-	-	-
Leicher	10.6	-	-	-	-	-
Control cases of present series	10.01	8.9	11.4	4.75	2.66	6.31

L.V. = Lowest Value.
H.V. = Highest Value.

Howland, Kramer, and Tisdall (27) found marked constancy of serum calcium in healthy children, the values lying between 10 and 11 mgs. per cent. Jones and Nye (21) gave the average plasma calcium as 10 mgs. per 100 ccs. Leicher found that, in healthy individuals of the same age, the serum calcium showed little variation, and gave 10.6 mgs per cent as the average during the first twenty years of life. Wills gave the generally recognised limits as 9.5 to 11.5 mgs. and in her own series found that the average value was 10.4 mgs., the range being 10.1 to 11 mgs. per cent.

With these figures the control estimations of the present series are in agreement both as regards the average serum values and the range of normal variations. The subjects of these control observations were children in the later stages of convalescence from various acute illnesses, together with a number of cases of alopecia areata who presented no other sign of disease. The detailed blood analysis is included in Table L./*

* [All the Tables will be found together after the Bibliography.]

In nephritic subjects (Tables II, III, IV) the serum calcium was found to be decreased during the more acute stages increasing subsequently as the general condition of the child, judged clinically, improved. This increase is apparent in the majority of the cases in which a series of estimations was made, but is particularly well illustrated by Cases 5 and 12 (Table III). The lowest values were found in two cases of chronic nephritis, one of whom developed Chvostek's sign when the serum calcium was in the region of 4 mgs. per cent. In the other case the serum calcium was reduced to 3.7 mgs per cent a few days before death but no facial phenomenon could be elicited.

Three sets of figures were obtained showing the decrease in calcium becoming more marked as the illness progressed (Table IV). It is apparent that this diminution is a slow process occupying at least several days, and the same tardiness is shown during recovery, the serum calcium slowly returning to normal in the course of several weeks.

The figures for serum inorganic phosphorus are in general agreement with those of other observers. During the more acute stages of illness the phosphorus values were higher than those found later on, but in very few instances was the serum phosphorus above the limit of normal range. Again, the highest values were noted in the two cases of chronic nephritis, in one reaching a level of 16 mgs. per cent a few days before death, in the other attaining a maximum of 13.3 mgs. per 100 ccs. The latter child, contrary to expectation and contrary to the recognised gravity of such a high serum phosphorus made a good recovery, and when seen six months later was in good health although albuminuria was still present.

The reciprocal relationship of the serum calcium and phosphorus/

phosphorus is very well shown in two of the three cases in Chart I.* The serum Ca., serum inorganic P., blood non-protein nitrogen and CO_2 values have been graphed so that their relationship to one another may be more easily appreciated. It is evident that in presence of severe acidosis, as judged by the CO_2 content, the serum calcium is reduced, the graphs of CO_2 and Ca. in all three cases showing close relationship. Likewise, there is some parallelism between the non-protein nitrogen and serum inorganic phosphorus, which, however, is not nearly so striking as the Ca.-CO_2 relationship.

There are not available sufficient figures to justify any discussion on the variations of calcium and phosphorus in the blood, and no new facts have been elicited. The main point of any reference to blood values is to emphasize that in this respect the present investigation was in complete accord with the reports of other observers.

*All the Charts will be found together after the Bibliography.

- - - - - - - - - -

II.

The Utilisation of Calcium and Phosphorus in Nephritis.

Previous references: In view of the attention which has been paid to the variations in the serum values of calcium and phosphorus in nephritis, it is rather surprising to find that the metabolism of these substances has not been investigated further.

Marriott and Howland (30) in 1916 published a paper on "phosphate retention as a factor in the production of acidosis in nephritis". They realised the presence of some upset of acid-base equilibrium and noted diminished urinary excretion of ammonia. Having eliminated acetone bodies as a causal factor in production of the acidosis, there being none of these in the urine, they suggested the possible implication of lactic acid, and passed on to focus attention on the renal excretion of NaH_2PO_4. Regulation of acid-base equilibrium of the body being maintained mainly by the ability of the kidney to excrete NaH_2PO_4, interference with this function would inevitably result in acidosis. As proof of the occurrence of this failure in renal excretion they demonstrated accumulation of inorganic "phosphate" in the blood, at the same time confessing that while in marked nephritis there was a tendency to this increase, yet death from nephritis sometimes occurred without any rise in "phosphate" and without evidence of acidosis. They also pointed out that the acidosis might be overcome without any corresponding change in serum phosphorus level. The opinion was expressed that "retention of acid phosphate", which normally constituted approximately 90% of urinary phosphate, would be sufficient to account for the acidosis. No generalised salt retention, in which the phosphate would of course participate, was found. Finally in support of the opinion that increase in blood "phosphate" was not the result of acidosis they pointed out the absence of any such increase in the serum of diabetic patients.

This paper has been quoted in most of the other publications on Ca. and P. in the blood in nephritis since 1916. The hypothesis of a "retention of phosphate" has found general acceptance, and indeed has been supported by the corroborative evidence of diminished urinary phosphate. Marriott and Howland themselves noted this.

In 1917 Halveson, Mohler, and Bergeim (13) published some observations on the calcium content of blood serum in various pathological conditions. They found distinctly decreased values in haematogenous jaundice, eclampsia, pneumonia, and in uraemia, in which the decrease was particularly marked. They noted a low urinary excretion of calcium in severe nephritis, and found only slight increase followed administration of calcium lactate. In the acidosis of pernicious vomiting of pregnancy alkali therapy led to decrease in Ca. excretion, the urinary calcium falling to 8 per cent of its previous value. From this it would appear that the decrease in urinary Ca. in nephritis cannot be a result of the acidosis. They, also, decided, from consideration of their urinary analysis, that acidosis in renal disease was due to retention of acid, not to excessive production, and suggested the possibility of a retention of both calcium and "phosphate" in nephritis.

In the perusal of many papers dealing with the variations of Ca. and P. in this disease no other reference to such a possibility has been met with. It stands alone, but is considered worthy of particular mention in view of the balances found in the course of this study.

Since Marriott and Howland first called attention to the subject, many others have commented on the increased serum inorganic phosphorus, decreased serum calcium, and diminished renal excretion of Ca. and P. in nephritis. The accepted explanation of these abnormalities was based on the inability

of/

of the nephritic kidney to excrete phosphorus. This was supposed to result in retention of the latter in the blood, and in an attempt to remove the excess of phosphorus there was increased excretion of calcium, presumably by the intestine. Hence the low serum Ca. values.

For a number of years no doubts were expressed as to the integrity of this theory of retention of phosphorus. Balance experiments, such as have been performed during the past ten years on cases of rickets, diabetes mellitus, and epilepsy on ketogenic dietary treatment do not seem to have been carried out. Yet, even if only to confirm the "retention of phosphate", they would appear to be advisable. Taking into consideration the experience of metabolic disturbance in other conditions, a healthy scepticism in regard to the above theory would be entirely justified. Hyperglycaemia in diabetes mellitus is not associated with retention of sugar in the body, and without determining the phosphorus balance in nephritis the possibility of a similar occurrence in this disease must be seriously considered.

Weight is added to this suggestion when one thinks of the distribution of phosphorus in the blood and the limited extent of present day knowledge as to its metabolism. Byrom and Kay estimate the inorganic P. to be about one twelfth part of the total blood phosphorus, and vast stores are available for the production of an increase. Of the skeleton both Ca. and P. are essential components, and in recent years it has been shown that phosphorus is intimately associated with carbohydrate metabolism, implying intimate association with the muscles. The uncertainty of assuming retention, from increase in such a small fraction of the total body phosphorus as that represented by the serum inorganic P. must then be obvious.

Taking the same line of argument with regard to the diminution/

diminution in serum calcium, deficiency of Ca. becomes a matter of some dubiety. Does the low serum level mean increased excretion and depletion of body calcium? Again the tremendous store of available calcium in the bones is forcibly suggested.

Nevertheless, until 1926 no balance experiments seem to have been undertaken in nephritis. In that year Boyd, Courtney and McLachlan[4] published a series of observations in nephritic patients. They found that nephritic children had a positive calcium balance unless the intake was very low, slightly higher than the minimal on which normal children showed a positive balance. The Ca. balance was independent of the blood calcium content. Oedematous subjects all showed a positive "phosphate" balance, except two on minimal intake; while non-hydraemic patients had in most instances negative balances, "extraneous factors" explaining the exceptions. They concluded that "evidence of phosphate retention given by blood and balance studies does not always agree".

These observations must be looked upon with caution, as the duration of the balance periods was in each case only two or three days. Findlay, Paton and Sharpe[11] have demonstrated the fallacies of such short periods. Apart from this, however, Boyd, Courtney and McLachlan did not quote control observations of their own, using for comparison with their nephritic results the figures of Sherman and Hawley.[40] Their findings give added point to the above remarks on the inadvisability of judging retentions from blood observations. They also suggest that the Ca. and P. balances in nephritis would bear further investigation.

Observations: During the past year, the calcium and phosphorus balances have been determined in a number of children suffering from nephritis. The result of this study is now to be considered. In each case clinical and biochemical data gave evidence of nephritis/

nephritis. The procedure followed was similar to that observed in other balance studies conducted in this hospital. Diet was confined entirely to milk, an approximate quantity of 100 ccs. per kilo of body weight being allowed daily. Where the quantity, so calculated, was thought to be too bulky, some of the milk was replaced by sugar in order that the caloric value might be maintained. In each case the child was put on the selected diet for a period of at least three days prior to the commencement of collection of excreta.

Balance experiments must ever be open to criticism until some method of marking the faeces is introduced, whereby collection of the appropriate specimens may be made with certainty. Bergeim's[1] suggestion, that a carmine capsule be given with the first and last meals of the period, the faeces being collected between the coloured parts and including the first, was tested in several normal children. The carmine was found to be spread over the intestinal evacuations of 48 hours, and the method accordingly was abandoned. In cases where there was a tendency to constipation, lavage was used daily. In all cases rectal lavage, with a quantity of sterile water, before and at the end of each period was practised.

Balance studies were carried out on twelve nephritic children. In one of these the procedure was designed specially to show the method of excretion, no special attention being paid to the amount of retention. It will be considered in the section dealing with excretion of Ca. and P. in nephritis. There are therefore eleven children in whom the quantitative balances of CaO and P_2O_5 were determined mainly from the viewpoint of "phosphate retention". These subjects represented various phases of renal involvement. Nine were cases of "acute nephritis", by which is meant an acute illness characterised by several of the following symptoms and signs: headache, vomiting/

vomiting, oliguria, oedema, increased blood pressure, albuminuria, haematuria, presence in the urine of casts, high blood non-protein nitrogen, increased serum inorganic P. and decreased serum Ca. They have been classified as "acute" since clinical recovery seemed complete within three to six months. The two remaining subjects suffered from chronic interstitial nephritis accompanied by dwarfism (Case 6) and chronic parenchymatous nephritis (Case 4).

In four of the acute cases a second balance period was observed after an interval varying from one to four months.

Case histories are given in Appendix II, the details of the analyses in Table V, and the methods of analysis in Appendix I.

Control figures were obtained from three children just before dismissal from hospital after recovery from acute ileo-colitis, bronchitis, and acute rheumatism. In addition, the calcium and phosphorus balances were ascertained in two cases of diabetes mellitus. There are therefore available the figures of 22 balance studies in 16 children, fifteen being those found in examination of eleven cases of nephritis.

Examination of the tabulated details of the balance periods brings to light a considerable amount of information. Some of this has been discussed by previous workers in other conditions, but so far as nephritis is concerned most of it is entirely new.

Since the main object of these investigations was to make some observations on the phosphorus balance, the retentions of CaO and P_2O_5 will first be considered. It has been shown by Telfer (43) that the balances of CaO and P_2O_5 in healthy children are approximately equal. In a report of "the mineral metabolism in coeliac disease", published in 1928, he states that young healthy children on a diet of fresh cow's milk have approximately equal retentions of CaO and P_2O_5 varying

from/

from 0.06 to 0.12 gms. per kilo of body weight per day. Sherman and Hawley (40) observed that in children, between 3 and 12 years of age, on a mixed diet with 750 ccs. of milk daily, the average retention of CaO was 0.01 gm. and of P_2O_5 0.008 gm. per kilo per day. They found that when the milk allowance was increased, the retentions of CaO and P_2O_5 rose. Therefore, since each child of the present series was having considerably more than 750 ccs. of milk daily, the retentions might reasonably be expected to show values over 0.01 gm. per kilo per day.

Macrae, (29) working in this laboratory, found that in convalescent children between 3 and 12 years of age on a diet consisting entirely of milk, the retentions of CaO and P_2O_5 were approximately equal and ranged between 0.016 and 0.052 gms. per kilo per day. (To avoid repetition, hereafter all retentions will be merely stated in gms. on the understanding that they have been calculated in terms of body weight for one day.) The three control subjects of this series showed a similar state of affairs, varying between 0.037 and 0.087 gms. (Table VI).

It is of importance, before passing on, to emphasise that Telfer (42) found in young healthy children retentions as high as

Observer	Age. in Yrs.	Subjects	Diet	Retention per day per Kilo in gms. CaO	P_2O_5
Holt, Courtney, Fales	-	Healthy infants	Modified milk	.09	-
		Young children	Mixed	.055	-
Sherman & Hawley	3-12	Nor.Chil.	Mixed +750 ccs.milk.	.01	.008
Telfer	-	" "	Milk only	.06	.12
Macrae	3-12	" "	Milk only	.016	.052
Present Series	6-7	Con. "	Milk only	.037-.081	.037-.071
	5-12	Neph. "	Milk only	.077	.096

Nor.Chil. = Normal Children. Con. = Control

Neph. = Nephritic.

.12 gm./

(17)

.12 gm., and Holt, Courtney and Fales, working with healthy infants, retentions averaging .09 gm. These being the highest figures recorded for healthy children, it might be expected that, in presence of any "retention" of calcium or phosphorus in the nephritic subjects of this series of observations, the balances would be at least as great.

A glance at the retention figures (Table V) will show that this expectation was not realised. The highest figure of the series was .096, the remainder being less than .08 gm. The table above facilitates comparison of these observations with those of other workers on the calcium and phosphorus balance in childhood.

In these fifteen determinations the balances varied to a marked extent. In eleven the CaO balance was positive, in four negative; while the P_2O_5 balance was negative on three occasions. The reason for these variations is not at all obvious. To quote once more Holt, Courtney and Fales, an intake of less than .09 gms. of CaO per kilo per day will produce either a very low retention or a negative balance. The intake in this series averaged .14 gms. CaO and .183 gms. P_2O_5. It would therefore seem that the supply of both was adequate. That the retentions had no relationship to the intake is best shown by graphing their respective values (Chart II). It is seen that the cases showing negative balance were adequately supplied, more so in fact than in some other instances. Similarly, the higher retentions are shown to be quite unconnected with the relative intake.

Neither the age nor the weight of the children could be correlated with the balances of either CaO or P_2O_5.

In the four cases in which balance periods were observed on two occasions, the retentions during the second period were diminished (Table V). In one of these (Case 3) the second period coincided with a mild exacerbation of the illness, and the/

the difference in the balance figures might well be attributed to the slight decrease in intake. In each of the other three cases, however, this explanation is not feasible, for two reasons - (1) the intake during each period was practically identical; (2) the decreased retention was very definite and of such magnitude that in two of the children a negative balance was found. These latter figures were obtained while the children were definitely convalescent, and it may be significant that the only other negative balances were found in two other convalescent children.

This, on the face of it, might be adduced as evidence in favour of a "retention" of both calcium and phosphorus in nephritis, the diminished retention during convalescence being pointed to as an indication that normal excretion by the kidney had been resumed, and was hard at work removing the excess accumulated during the acute stage. This argument is scarcely admissible when the normal retentions of the previous periods are considered, and some other explanation seems to be demanded. An attempt will be made to answer the question when the excretion is dealt with.

Attempts to correlate the retention figures for CaO and P_2O_5 in each child with the urinary analysis and approximately contemporary blood observations were of no avail (Charts III & IV). The level of serum calcium had no bearing on the CaO retention, nor had the serum phosphorus any on the P_2O_5 balance. In this, entire agreement was shown with the observations of Boyd, Courtney and McLachlan,(4) namely that "the calcium balance is independent of the blood Ca content", and "evidence of phosphate retention given by blood and balance studies does not always agree". The graphs well illustrate this lack of relationship. To select an outstanding example, Case 4 with serum Ca. of 5·9 mgs. per 100 ccs. retained .044 gms. CaO. Her serum P. was 12.mgs. per 100 ccs: P_2O_5 retention .054 gms. That is,

the/

the blood findings were markedly abnormal while the retention figures were normal.

Similarly, the levels of blood non-protein nitrogen (N.P.N) and chloride (Cl) could not be associated with the CaO and P_2O_5 balances (Table VII). Nor was any connection found between the balance and the urinary excretion figures, irrespective of whether the latter were expressed as gross excretion or as excretion per kilo per day (Charts III & IV).

In all the nephritic subjects the CaO and P_2O_5 excreted by the urine was found to be much less than in the control cases. This held for urinary excretions whether expressed in terms of percentage of intake or as gross output, and will be discussed in detail later. The main part of the total CaO and P_2O_5 recovered appeared however in the faeces.

The remaining point shown by the balance studies in nephritic children is the remarkable equality in retention of CaO and P_2O_5. This has been demonstrated in healthy subjects and in other pathological conditions. Reference has already been made to the subject, Telfer, and Sherman and Hawley having noted it in healthy children; the former also finding it in coeliac disease. Nelson observed this approximate equality in epileptic children undergoing ketogenic dietary treatment. It has been found in cases of rickets, and apparently there is no exception to the rule in nephritis. The balance experiments of Boyd Courtney and McLachlan, while not demonstrating this in all cases, do so in several instances, but it must be remembered that their observations were of short duration extending over two or three days. The balance figures for the present series of cases show definite close relationship. This is most easily appreciated when the respective retentions of CaO and P_2O_5 are graphed (Chart II). Taking this fact into consideration, it is obvious that even if "retention of Phosphate" did occur in nephritis, an approximately equal retention of calcium would accompany it.

From these observations alone the suspicion would arise that the increased serum inorganic P. and decreased serum Ca. are the results of an abnormal distribution in the blood rather than those of an error in retention. As has been already indicated in the first section of this work, abnormality in the phosphorus distribution in nephritis does occur. Thus blood and balance studies are in entire agreement, the former indicating that the internal variations in P. distribution are not an index of increased retention; the latter showing that increased retention does not play any part in the phosphorus metabolism of the nephritic subject.

Recapitulating the conclusions arrived at so far, it is taken as having been satisfactorily shown that in nephritis:-

1. The retention of CaO is as a rule positive and not abnormally high.
2. The retention of P_2O_5 is as a rule positive and not abnormally high.
3. As in normal children and in certain other diseases the balances of CaO and P_2O_5 are approximately equal.
4. There is no connection between the serum levels of calcium and inorganic phosphorus on the one hand, and the balances of CaO and P_2O_5 on the other.
5. There is no relationship between the retention and the urinary excretion of either CaO or P_2O_5.
6. The majority of the recovered calcium and phosphorus is found in the faeces, urinary excretion being reduced in every case.
7. In view of Byrom and Kay's demonstration of the altered distribution of phosphorus in the blood, taken in conjunction with the balance studies, it is no longer permissible to entertain the idea of a "retention" of phosphorus.

- - - - - - - -

III.

The Absorption of Phosphorus in Nephritis.

Historical: In the past, absorption of inorganic substances has been assessed mainly from consideration of the results of balance experiments. This is particularly true with regard to phosphorus. Comparatively few references have been found to observations on blood phosphorus after oral administration of phosphate, and none of these apply to nephritis.

It seems to have been generally assumed that absorption of phosphorus in this disease was normal, or at least satisfactory. How else could there have been a "phosphate retention". The majority of the balance studies already reported justify this assumption, but of the fifteen, two balances were barely positive and other three were negative. These five suggested that phosphorus absorption should be investigated, since a low positive or a negative balance might have been produced equally well by either poor absorption or excessive excretion.

As has been already remarked, four of these five balances in question were observed in convalescent children. Altogether the P_2O_5 balances were estimated twice in four cases of nephritis, the first period being observed during the more acute stage of illness, the second during convalescence. In every instance the retention found in the convalescent period was lower than previously, and the P_2O_5 excreted in the urine had increased.

(47)

Wills Sanderson and Paterson, referring to calcium excretion by the urine, stated that even in presence of a negative balance, where there is increase in the urinary Ca. it is fair to conclude that there is increased absorption. Since urinary excretion of Ca. and P. run more or less parallel, this dictum should apply also to phosphorus absorption. Therefore it would seem that, since P.excretion in the urine had increased at the time of the second balance period in the four cases mentioned above, P. absorption/

absorption must also have improved. This implies that the absorption of phosphorus is not up to normal standard during the acute stages of nephritis, but improves as recovery proceeds.

If, for the moment, this is assumed to be the case – poor absorption in acute nephritis – then a simple explanation of the lowered urinary excretion is apparent. Poor absorption will supply little more than the needs of the organism and comparatively little excess P. will remain to be excreted. If however absorption is normal, then the occurrence of diminished renal output must be explained otherwise. Therefore, before renal function, in respect of P. excretion, can be said to be impaired, it must be shown that phosphorus is absorbed in approximately normal fashion thereby providing the kidney with P. to excrete.

The key to the problem lies in the determination of the state of P. absorption in different stages of the illness, and in this study an attempt has been made to investigate the question by means of blood curves. As with absorption of other substances, e.g. glucose, such a study does not give information relative solely to absorption. Nature being ever on the alert to correct any alteration in the equilibrium of the organism, it follows that any induced increase in concentration of a component of the blood automatically leads to increased activity of the regulating mechanism.

Any increase in blood phosphorus after oral administration of phosphate must be regarded as an indication of the activity of absorption. The amount of increase and its duration will depend on the speed and power of the regulating mechanism. A slow increase in the blood curve may be the result of either subnormal absorption or supernormal sensitiveness to increase. The reverse, rapid and prolonged increase, can be explained as well by dulling of the regulating mechanism as by extra-activity of the absorptive process.

The/

The present series of curves has been obtained from estimations of serum inorganic phosphorus at fixed intervals after ingestion of NaH_2PO_4. It may seem curious that absorption may be judged from changes induced in this small fraction of the blood P. while "retention" may not. Kay and Byrom[6] have shown that increase in inorganic phosphorus of serum in nephritis is accompanied by corresponding diminution in the organic P.of the corpuscles, the total P. remaining practically unchanged. After phosphate ingestion, however, increase in serum inorganic P. has a different significance, and from previous evidence, to be detailed immediately, it seems justifiable to assess phosphorus absorption on this increase.

Wigglesworth and Woodrow[45] in 1924, while studying "the relation between the phosphate in blood and urine", found that in healthy subjects an increase of 55-60 per cent occurred in inorganic blood P. after ingestion of 25 gms. of acid or alkaline phosphate. The organic fraction of the acid-soluble P. which comprises the main part of the organic blood P., remained unchanged and can accordingly be left out of consideration. They found that as a rule the "inorganic phosphate" was equally distributed between plasma and corpuscles, which means that increase in blood inorganic P. was as a rule evident in both. When the inorganic P. of plasma was far above normal, its concentration in the corpuscles was lower but still increased. Therefore it would seem that any increase in blood phosphorus will be shown by estimation of the inorganic P. of the serum, although the reverse is not necessarily correct - that increase in serum P. is indicative of increased blood phosphorus, a state of affairs which has been dealt with previously.

Two methods of investigation have been used by previous workers. These were (1) prolonged administration of phosphate with/

with serum P. estimations every few days, and (2) observation of blood curves. The former was employed by Salvesen, Hastings and McIntosh (37) while working on "the blood changes and clinical symptoms following oral administration of phosphate". They found that, when continued over a long period, small doses of neutral phosphate produced increase in serum "phosphate" and fall in serum Ca.: Alkaline phosphate led to slight increase in serum "phosphate" but no alteration in Ca.: while acid phosphate induced marked increase in the "phosphate" with again no change in the Ca. of the blood serum.

The value of observations on blood concentrations after prolonged administration must be regarded as doubtful. As already suggested, the body will have become accustomed to the new conditions and have made the necessary adjustment in metabolism, and in addition the time of withdrawal of the specimens must be carefully regulated. Blood withdrawn shortly after a meal will show a subnormal level, and that taken after a dose of phosphate an increased value for serum inorganic phosphorus. It is much better to make serial observations at short intervals.

This was the procedure followed by Murdoch (32) in her investigation of phosphate absorption in normal and rachitic children. She observed a variable increase in the inorganic P. of blood serum after oral administration of NaH_2PO_4 gms. IV. In normal subjects the average rise was 2 mgs. per 100 ccs., and had attained its maximum in the course of two hours. There was subsequently a sharp fall in concentration, which however, had in every case failed to restore the fasting level in 4 hours. In rickets the form of the curve was found to vary with the phase of the disease. During the active stage the curve obtained was similar to that of normal subjects, being of course at a lower level. In the healing stage a tremendous rise

was/

was found, approximately three times that in the controls, and from this Murdoch concluded that "in healing rickets, absorption of phosphorus may be three times as great as in health." In support of this contention, the increased retention of P. found in the healing stages of rickets was quoted.

In the present enquiry, Murdoch's procedure was adopted. Each child was fasted for a minimum period of three hours, at which point the fasting specimen of blood was obtained. Four grams of NaH_2PO_4 dissolved in approximately 100 ccs. of water were then given, and samples of blood withdrawn at one, two, and four hour intervals. Estimation of serum inorganic P. was carried out immediately after procural of each specimen. In a number of cases, absence of a suitable vein, presence of much oedema, or the temperament of the child prevented the observation of blood curves. During the course of the investigation both solids and liquids were temporarily suspended.

Observations: Twenty blood phosphorus curves were obtained from 15 nephritic children. Control curves were observed in nine children convalescent from other diseases, mainly chorea and rheumatism. The figures appertaining to these observations are given in Tables VIII and X.

The control curves show a good deal of variation in detail, but closely resemble Murdoch's normal series in children of the same age - 6 to 12 years. The fasting level varied in different individuals from 4.6 to 6.3 mgs. per 100 ccs., i.e. throughout the normal range. In all, definite increase in the serum inorganic P. was found one hour after administration of the phosphate. In six cases (Chart VI) the maximum rise was shown at this time, in three (Chart VII) it occurred at two hours. At 4 hours in every instance the return to fasting level was well advanced, but in none had the latter been reached/

reached. The increase varied in amount as in time of attaining a maximum, the range being 0.75 to 3.2 mgs. per 100 ccs., and there did not seem to be any relationship between the height of the curve and the fasting level (Table VIII). Three of the subjects of these control curves were also used as controls for the nephritic balance experiments. As will be seen from the following table, the rise in the curve gave no indication of the retention found. Nor did it indicate the percentage of the intake which would be excreted by the urine, except that in these three instances, the smaller the increase in the blood curve the higher the percentage excretion by the urine.

Case	Age in Years.	Increase in P. curve.	P_2O_5 retention	% age of P_2O_5 intake excreted in urine.
C.H.	7	1.85 mg.p.100ccs.	.077 gm.p.K.p D	48.8
E.McL	6	2.7 "	.046 "	42.7
J.K.	6	3.2 "	.037 "	33

This might be explicable on the assumption that the lower curves indicate a more active renal excretion and occur as a direct consequence of the latter. Such an assumption is not warranted on this small number of observations.

Failure of all these curves to regain fasting level in four hours aroused interest, and several curves were prolonged for periods varying up to 14 hours in an attempt to find how long a time would elapse before fasting level was again restored. These observations were made in three convalescent rheumatic cases, one case of cardiac decompensation, and a case of diabetes mellitus under insulin treatment. The figures for these observations are detailed in Table IX. As will be seen (Chart VIII), two of the rheumatic cases had almost regained fasting level in 13 and 14 hours respectively. The third, falling at 5 hours, rose again, and at 10½ hours was almost as high as at any part of its course, well above fasting level/

level. The cardiac case showed considerable elevation remaining at 7 hours, but owing to the clinical condition of the child the observations could not be prolonged further. The curve of the diabetic subject was rapidly approaching its starting point at 7 hours.

Wigglesworth and Woodrow,(45) in work already referred to, found increase in the blood inorganic P., persisting 10 hours after a large dose (25 gms) of acid or alkaline phosphate, in healthy adults. Not only did it persist, but having reached a maximum elevation in one hour, no decrease was found in frequent estimations made throughout the day.

This persistence of increase in inorganic P. of blood or serum does not seem to have attracted much attention. Wigglesworth and Woodrow have suggested that phosphate behaves as a threshold substance and is excreted by the kidney only when the blood concentration exceeds a certain, undetermined value. This may explain the type of curve found by them, but it does not assist in the explanation of the slow, more or less steady fall extending over 10-12 hours found in the control cases of the present series. Bergeim suggested that phosphorus was freely absorbed throughout the intestinal tract, and although Wigglesworth and Woodrow found continued steady elevation of blood inorganic P., they also found an accompanying increase in urinary excretion, which of itself supports Bergeim's contention.

Even if this is the case, that phosphorus is absorbed throughout a great part of the intestine, it is curious that the blood P. should be allowed to remain elevated for a period of four to twelve hours in healthy subjects. That the regulating mechanism is able to cope with a much larger increase than any induced by oral administration of phosphate has been proved by the work of Brain and Kay who found that, in healthy adults, intravenous injection of 0.55 gm. P. in the form of sodium/

sodium glycerophosphate led to additional excretion in the urine of at least 0.15 gm. P. within two hours. The majority of their subjects excreted much more than 0.15 gm. P. in this time, thereby showing that on occasion renal excretion can be tremendously increased.

It would therefore appear that the phosphorus-regulating mechanism is apathetic except in presence of a very marked increase in blood phosphorus, even in normal subjects.

Absorption curves in nephritis:

In fifteen nephritic subjects very similar results were obtained. Table X has been compiled from the observations of 22 curves in renal disease. The fasting level varied between 4 and 12 mgs. per 100 ccs., nine being over 6 mgs. In 13 of these curves the maximum rise occurred at 1 hour, and in all it had been reached before 2 hours, as in the controls (Charts IX, X, XI). Again there was great variation in the amount of increase in serum inorganic phosphorus, the range corresponding to that of the control series, and as in the latter, no relationship could be found between the fasting level and the height of increase in the curve. This is well illustrated in Case 12 from whom three curves are available for study (Chart IX). The first, observed during an acute exacerbation of a chronic nephritis, showed a fasting level of 12 mgs. and rise of 1.33 mgs. per 100 ccs. The second, in early convalescence, showed the fasting level to be 9.2 and the rise 0.8 mgs. per cent; while the third, some time later, had a fasting level of 6.15 and a rise of 1.1 mgs per cent.

Nor could the P. curves be correlated with the clinical condition. Case 12, on each of the three occasions when curves were carried out, showed the same type of curve. The maximum rise was attained in 1 hour and remained steady at 4 hours. Improvement in his renal function, which had undoubtedly taken place/

place, was not accompanied by more rapid fall in the blood P. curve, and since Wigglesworth and Woodrow found this type of curve in healthy adults, although after a much larger dose of phosphate, it can hardly be labelled "abnormal".

Similarly presence of oedema was apparently of no significance so far as the P. curve was concerned. Case 4 showed a similar curve to that found in Case 12 and J.D., who had no oedema. D.B. and Case 9 with great oedema showed very similar curves which differed from the above in that there was a fall at 2 hours, with subsequent increase. E.M., again with much oedema, showed a third type of curve attaining a maximum at 2 hours and falling to almost fasting level at 4 hours.

On the whole, the nephritic curves compared very favourably with normal curves from the point of view of absorption, even when the serum inorganic P. was in the neighbourhood of 12 mgs. per 100 ccs., a state of affairs generally regarded as indicative of death within a few weeks. Comparison is facilitated if the figures are tabulated. It will be seen that the average fasting

Type of Case	Number of Curves	Average Serum Inorg.P. in mgs. % Fast.level	High.level	Incr.	Lowest increase	Highest increase
Murdoch's normals.	3	5.3	7.1	1.8	1.6	2.2
Control subjects.	9	5.25	7.05	1.8	0.75	3.2
Nephritic subjects.	22	6.22	7.58	1.36	0.65	3.43

Fast. level = Fasting level.
High. level = Highest level.
Incr. = Increase.

level, highest level attained, and increase in the control subjects of the present series of observations are in absolute agreement with Murdoch's normal curves. In the nephritic subjects the fasting levels when averaged are higher, as are the/

the maximum elevations; but the increase is not quite so good, being about 25% lower. The range, however, is very similar in the control and nephritic cases of this series.

With regard to the lowered P_2O_5 balances observed in the four repeated balance studies, the absorption, as judged by the curves cannot be held responsible (Table XI). Case 3 showed on each occasion an increase in serum P. of 2 and 2.29mgs. per cent: Case 8 2.05 and 2.65 mgs. per cent: and Case 9 1.8 and 1.7 mgs. per cent. In the other case (5) it was not possible to determine the earlier P. curve, but that corresponding to the second balance period showed an increase of 1.7 mgs per cent.

Comparison with the P_2O_5 balance figures and the percentages of intake excreted by the urine shows that there is no correlation between these and the rise in phosphorus curve (Table XI). Of the series in which both blood curves and balance studies were carried out, Case 8 showed the highest rise in the curve - 2.65 mgs. i.e. well above the average normal rise of 1.8 mgs. per cent - while showing a minimal retention of P_2O_5. It is evident that the inverse relationship shown by the three control curves, and already referred to, does not hold in nephritis, even as it may not be true for a larger series of normal subjects.

If then, the information obtained from these blood phosphorus curves is briefly summarised, it appears that:-

<u>In the control curves:</u>

1. The increase in serum inorganic P. after ingestion of NaH_2PO_4 gms. IV, reaches its maximum within 2 hours, and thereafter slowly falls.
2. The amount of increase has no relation to the fasting level and averages 1.8 mgs. per 100 ccs., with a range of 0.75 to 3.2 mgs.
3. The increase does not give any indication of the retention of P_2O_5, or of the percentage of intake of P_2O_5 appearing in the urine.

In nephritic subjects:

1. The increase in the phosphorus curve also attains its maximum within 2 hours, but shows more variation in rate of fall.
2. The amount of increase has no relationship to the fasting level, and while showing a lower average of 1.32 mgs., still shows the same range of 0.65 to 3.43 mgs.
3. Neither the severity of the illness, as judged clinically, nor the presence of any particular manifestation of nephritis has a constant effect on either the height or general form of the P. curve.
4. There is no correlation between the blood phosphorus curve and either the retention of P_2O_5 or the percentage of intake excreted by the urine.

Therefore, it is difficult to see how any conclusion can be arrived at other than this, that in so far as can be judged by blood curves, the absorption of phosphorus in nephritis is satisfactory and compares favourably with that in normal children.

- - - - - - - - - - - - - - -

IV.

Absorption of Calcium.

Historical: The balance investigations of this study showed low urinary excretion of calcium. This has been observed on many previous occasions, and references to its occurrence are fairly frequent throughout the literature on nephritis. The decrease has been attributed to impairment of renal function occurring as a manifestation of the presence of diseased kidneys, without, as in the case of phosphorus, any accumulation in the blood. Boyd, Courtney and McLachlan concluded, from their balance studies on nephritic children, that the nephritic kidney was incapable of excreting calcium in normal fashion, indicating as evidence of this the lowered urinary content, and the abnormally small amount of calcium per 100 ccs. of urine.

Again, before diminished excretion can be made responsible for the lowered urinary calcium, it must be shown that absorption is comparatively normal, and this aspect of Ca. metabolism in nephritis has, so far as can be ascertained from the literature, received but scant attention. An attempt has been made, in the course of this investigation, to remedy the defect; but before discussing the results, a brief summary of the work done by others on this subject would be advisable.

In studying the effect of ingested salts, on the blood Ca., two methods have been employed. The earlier results, from prolonged administration of Ca. salts, were extremely contradictory and inconclusive; but more recent observations, in which a series of estimations was carried out at intervals after a single dose, have shown much less variance.

The striking feature of the earlier reports on absorption of calcium is the stress laid on the difference in availability of different preparations of Ca. and it therefore seems necessary to give some attention to this matter. Steenbock Hart/

Hart, Sell and Jones[41] in 1923 decided that, so far as could be judged from rats, no difference in availability existed between calcium lactate, carbonate, phosphate, silicate or sulphate so long as a sufficient quantity was supplied. Jamsen[20] in 1924 found that Ca. lactate had no effect on the blood calcium, when given orally, but found increase with calcium chloride and bicarbonate, the effect of the latter being much more marked. Hjort[16] in 1925, was of opinion that the more soluble salts, the lactate, chloride, and glycero-phosphate had a much more constant effect in raising the blood Ca. level than the less soluble salts such as the carbonate.

If the availability of the calcium depends on the solubility of the salt exhibited, then gastric acidity might be supposed to play some part in absorption, since with higher acidity a larger amount of the Ca. would be in solution. Wills, Sanderson, and Paterson[47] reported some work on this subject in 1925. They concluded that gastric acidity did not seem to be a limiting factor in the supply of calcium to the body. This opinion was based on the figures obtained from balance experiments, no observations on blood values being reported. Four years earlier, in 1921, Mason[31] had already noted that solution of calcium in weak HCl did not affect the rate of absorption. He also indicated that Ca. lactate produced less effect on the plasma Ca. than did $CaCl_2$, and consequently inferred that the latter was better absorbed.

Since different observers have favoured different salts, it would appear that there can be no marked difference in their availability. The more recent workers have shown that calcium lactate is an adequate source of supply for absorption studies, and it was accordingly selected as the preparation of choice in the present work. An additional point in its favour is the fact that no change in the pH of the blood, such as occurs with $CaCl_2$, follows its administration.

As/

As has been already mentioned, it was not until quite recently that general recognition was given to increase in blood Ca. after ingestion of calcium salts. The earlier workers relied mainly on prolonged administration to effect an alteration in the blood level. Bergeim (1) in 1917 noticed that in several cases of uraemia, with associated low serum calcium, administration of Ca.lactate led to clinical improvement with coincident increase in serum Ca. That the latter can be attributed to absorption of the calcium lactate is of course open to question, since it would in any case accompany clinical improvement without the aid of an extra supply of calcium by mouth.

In 1921, French workers (3), while studying the action of calcium as a reputed diuretic decided that the beneficial effects of $CaCl_2$ administration were produced by the Cl, the Ca. and its water being thrown off. Giving large doses (8-12 gms) of the salt to healthy subjects, on an otherwise salt-free diet, they observed great physical and mental depression. These symptoms may be attributed either to excessive increase in blood Ca. or to the acidosis induced by the acid absorption. As in Bergeim's observations, reported above, estimations of blood Ca. were either not carried out, or not taken at definite intervals, and the torpidity of the subjects was credited to the acidosis; the conclusion being that the calcium was thrown off, presumably in the intestine, and therefore not absorbed.

Similarly, Leicher (28) in 1923 after weeks of administration of various Ca. salts, failed to obtain any increase in serum Ca. In the following year Rockwood and Burrier (35) had parallel findings in nephritic subjects. They could not elevate the serum calcium by giving large doses of either the lactate or chloride of calcium.

About/

About the same time, Salvesen, Hastings, and McIntosh,[37] working with dogs, found that after ingestion of $CaCl_2$ in quantities sufficient to produce a severe uncompensated acidosis, the symptomatology could be explained by absorption of Cl_2 without the Ca. They failed to find increase in the blood calcium, but since examination of their figures shows that in one dog when estimation was carried out 1½ hours after a dose of calcium chloride, an increased blood value was observed, it seems probable that their failure was due to the time of withdrawal of the blood specimens. In two cases of nephritis, in human subjects, they observed no increase in the low blood Ca. subsequent to administration of calcium lactate orally.

As was indicated in the section on phosphorus absorption, these prolonged experiments are unsatisfactory owing to the tendency of the blood to restore the equilibrium of its constituents as soon as possible. Information obtained from serial observations at relatively short intervals after ingestion of a single dose of one or other of the calcium salts is much more constant and reliable. This method of investigation was employed by Mason in 1921. With a single large dose of calcium lactate (5 gms), he found very slight increase in plasma calcium values, but with $CaCl_2$ the effect was more constant and the rise greater. He therefore concluded that $CaCl_2$ was absorbed to a greater expent.[20] Jansen, in 1923, found temporary increase in blood Ca. after large doses of calcium bicarbonate and chloride, the rise being greater with the former salt.

In 1925, the first really satisfactory work was done by Hjort.[16] Studying the effect of ingested Ca. salts on the blood calcium of dogs, he found that the more soluble salts, when given in amounts containing 0.2727 gms. CaO per kilo of body weight, were absorbed rapidly enough to increase the serum Ca., whereas the more insoluble salts were inconstant in effect.

This/

This work was confirmed and applied to human subjects in the following year by Kahn and Roe,[22] and later by Bauer and Ropes.[2] The former found that, subsequent to administration of calcium salts orally, elevation of the blood Ca. was produced. With 20 gm. doses the average increase was 81%, reaching a maximum in 4-5 hours, and being maintained for a period of 4 hours. With 5 gm doses, the increase averaged 80%, attained its highest level in 6-7 hours, and was sustained for 1½ hours. They pointed out that these observations were in disagreement with the findings of many, that the serum Ca. could not be raised by oral administration of calcium.

Bauer and Ropes[2] confirmed the general findings of Kahn and Roe, but differed considerably in detail. They, also, found that in human subjects ingestion of Ca.lactate induced an elevation of serum Ca., 5 gm. doses producing a maximum increase of 14% in 1-4 hours. Larger doses were found to give more pronounced rise, 10 gms. being followed by a maximum increase of 28% in 1-5 hours. Irrespective of the size of the dose, they found that some elevation of serum Ca. persisted for a period of about twelve hours.

In 1927 Kahn and Roe[23] published some further work which agreed more closely with the observations of Bauer and Ropes. They came to the conclusion that 5 gms. of Ca. lactate was the optimum dose for investigations of this kind, or indeed for therapeutic purposes. Since Bauer and Ropes had allowed the subjects of their observations to have a light meal six hours after the dose of calcium, an investigation was made of the effect of food on the blood calcium curve, and it transpired that when various foodstuffs were given with the calcium, there was marked depression of the rate of absorption.

It appears, therefore, that absorption of calcium, in the form of the lactate at anyrate, definitely does occur in healthy human/

human subjects; although the behaviour of the serum Ca. after oral administration of the substance has not been shown to be at all consistent. Thus the maximum rise has been reported as varying between 14 and 81%, and its time of occurrence anything from 1 to 7 hours. Accordingly, before the absorption of Ca. in nephritis could be assessed, it was necessary to obtain some control curves for comparison both with those of previous workers and with those found in nephritis.

The procedure in all cases was as follows. Each subject was fasted for three hours prior to withdrawal of the fasting specimen of blood. Four grams of calcium lactate in approximately 100 ccs. of water was then administered, and subsequent observations were made on the serum Ca. at intervals of 2, 4, and 6 hours. No food or water was allowed during this period, since Kahn and Roe observed that food decreased the rate of absorption, and Hjort found that administration of 150-600 ccs. of water produced a decrease of 1 mg. in the serum Ca., the decrease persisting for about five hours.

The seven control curves (Table XII and Chart XII) show great similarity. In five the maximum elevation occurred at 2 hours, in the remaining two there was a further slight increase at 4 hours. In all, the return to fasting level had been well advanced by the end of 6 hours. None of these curves showed a final reading which was below the original level.

In nephritic subjects 28 curves were observed in 16 children. These showed numerous variations from the normal and from one another (Table XIII). In 22 curves the increase 2-4 hours after the dose of lactate compared favourably with that in the controls, while in four of these 22 it exceeded any rise shown in the latter series. In the remaining six curves the increase was less than that shown in four hours by the lowest of the control series. In all the nephritic curves there was some evidence of absorption. Admittedly several of the six low curves showed increases which were well within

experimental/

experimental error (0.5 mgs.%), but if the normal elevation of serum calcium be taken at either Bauer and Ropes' figure of 14% maximum, or at the average of 10.04% shown by the control curves of the present investigation, it is apparent that the increase to be expected (0.97 mg.%) is only a little more than the experimental error for the method of Ca.estimation. Since only small quantities of blood could be withdrawn on each occasion, duplicate analysis was not always possible, but where carried out, showed that the single estimations were fairly reliable.

It seems, therefore, that as in normal subjects, so in children suffering from nephritis, administration of a single dose of calcium lactate orally leads to elevation of the serum calcium. As has been already indicated, in the large majority of the nephritic curves the elevation corresponded to that in the control series, but much wider variation in the increase was noted. This becomes more obvious if the control and nephritic figures are contrasted, as in the table below, in which the average figures for the two groups are presented.

Type of Subject	Serum Calcium in mgs. per 100 ccs. No. of Curves	Average Fast.Level	High.Level in 4 hrs	Average increase	Average % increase	Low. incr.	High. incr.
Control Series	7	9.66	10.63	0.97	10.04	0.49	1.43
Nephritic Series	28	8.98	9.95	0.97	10.8	0.25	2.87

Fast.Level = Fasting Level.
High.Level = Highest level.
Low. incr. = Lowest increase.
High.incr. = Highest increase.

Since none of the control curves showed increase persisting after 4 hours, this has been adopted as the maximum time during which comparisons of absorption may be drawn, and the average increase in both cases is found to be exactly equal, 0.97 mgs. per 100 ccs. of serum. In four of the nephritic curves, the maximum increase did not occur until 6 hours, and if these figures/

figures be included in the average, the increase in nephritis becomes slightly more than in the normal - 1.11 mgs. per 100 ccs. of serum.

Of the five nephritic children in whom poor rise was found by four hours, two were subjects of balance studies (Cases 4 & 8). Although their blood Ca. curves seemed to indicate some defect in absorption, in both a positive CaO balance was found indicating again that the balance cannot be predicted from the type of blood curve. If the increase in the Ca. curve is contrasted with the retention of CaO and the percentage of CaO intake appearing in the urine, it will be found that no relationship exists between them (Table XIV). Three children (Cases 11, 8,&9) gave a negative balance, but the respective blood curves showed increases of 2,5, 1.0, and 0.52 mgs. per cent.Nor did the highest balance figure correspond with the greatest elevation in the blood curve. Similarly with the urinary excretion, case 9, while excreting only 1.13% of CaO intake by this route, showed a rise of 0.7 mg. in the blood Ca. curve. Some time later, when the urinary figure had risen to 2.68%, i.e. more than double its previous amount, the Ca. curve showed an increase of 0.52 mgs.%. This lack of relationship is shown also by the control subjects in whom both the CaO balances and blood curves were observed (Table XV). There was a tendency in these to a reciprocal relationship, but from such a small number of subjects it is not justifiable to consider it further.

Curves obtained during different stages of illness, however, show more definite indications of some upset in calcium metabolism, with gradual return to normal. In each of two children (Cases 5 & 12) three curves were obtained; and in other six (Cases 3,7,8,9,I.D., E.M.,) - two curves. This procedure was suggested by the change in retention found in convalescent children, and also by the altered disposition of the calcium excretion/

excretion. As will be seen from Table XIII, the increase in serum Ca. had no relationship to either the fasting level or the stage of the disease. Case 12, with fasting estimations, on two occasions, of 4.8 and 4.62 mgs. per cent showed corresponding elevations of 1.77 and 0.53 mgs. Case 5, with primary observations of 7.87 and 9.24 mgs per cent showed on each occasion an increase of 0.89 and 1.07 mgs per cent; i.e. an almost negligible increase in the height of the curve. E.M., with fasting levels of 7.91 and 9.27 mgs per cent, gave a greater rise - 1 mg. on the first observation then on the later one - 0.31 mg. In each case the later curves were observed after the onset of definite clinical improvement, and although the increase did not seem to be dependent on the fasting level, yet the type of curve obtained during different stages of the illness showed marked aberration from normal. This is most easily appreciated when the figures are graphed.

The graphs (Charts XII to XVI) have been arranged in groups entirely from their general appearance, since no other method of classification could be found. Four categories have been adopted.

(1). Curves very similar to the control curves (Chart XIII.) This includes two cases of acute nephritis with great oedema; two cases of acute nephritis during convalescence; and a convalescent chronic parenchymatous nephritis.

(2). Curves characterised by the occurrence of a fall in serum Ca. level at 6 hours of such magnitude that the final reading had fallen below the fasting level (Chart XIV). The subjects, in whom this was found, were one case of acute nephritis; six cases of acute nephritis in various stages of convalescence; one case of renal dwarfism; one case of functional albuminuria; and a case of chronic parenchymatous nephritis showing much oedema, ten days prior to the onset of a fatal pericarditis.

(3)/

(3). Curves in which a good increase was obtained at 2 hours, followed by a marked fall, reaching even lower than fasting level, at 4 hours, with a succeeding terminal rise at 6 hours (Chart XV). This group, also, shows some variety in its subjects viz. one case of acute nephritis with uraemia and some oedema; two cases of acute nephritis, one of which had oedema; two cases of acute nephritis during a rather slow convalescence; and one late convalescent case.

(4). A final group in which a variable increase was found at 2 hours, and 4 hours, with the maximum elevation shown by the 6 hours' specimen (Chart XVI). The cases falling into this category are :- one child just after the cessation of uraemic convulsions; one acute nephritis with generalised anasarca; one acute nephritis in early convalescence; and one chronic nephritis which ultimately left hospital comparatively well.

Thus in each group are found examples of the various stages of the disease, with and without oedema, which latter does not appear to have any constant effect on the behaviour of the calcium curve. If the curves observed in different stages of nephritis are followed, it is found that the one type of curve seldom occurs twice in the same child, suggesting that the balancing mechanism is not acting continuously in the same manner. Examination of the charted curves of other observers does not show variations to have been found in normal subjects similar to those just described in nephritis, and since the average increase in the serum Ca. value has been shown to be quite as large in nephritic as in normal children, absorption cannot be responsible for these abnormalities. Since the abnormal curves have been shown to vary from time to time in the one subject, they cannot be accepted as being the normal curves peculiar to the different individuals, and here, as in the case of blood phosphorus curves, the inference seems to be that there is upset of the internal metabolism of calcium.

Therefore/

Therefore the low urinary output of calcium found in nephritis cannot be the result of an alteration in absorption, and the factors producing it must be sought elsewhere. A resumé of the grounds for this conclusion follows:

In control subjects:-

1. The serum Ca. curve showed an average increase of 0.97 mgs., or 10.04%, occurring within 4 hours of the administration of Ca. lactate gms.IV.
2. As a rule the serum Ca. had almost returned to fasting level in 6 hours.
3. The serum calcium curve was independent of the fasting level.
4. The curves, when graphed, showed great consistency in form.
5. The increase in the Ca. curve had no bearing on the CaO balance; nor was it related to the urinary output of CaO.

In nephritic subjects:-

1. The Ca. curve gave an average increase of 0.97 mgs., or 10.8%, within 4 hours, but showed a greater range of variation than in the control subjects, which although in a few cases within the possible experimental error, was shown by the balance studies to be reliable as an indication of the activity of absorption.
2. The final reading at 6 hours was found to be extremely variable.
3. The curves demonstrated that the increase, induced in the serum Ca. level, was independent of the fasting estimation.
4. When graphed, many curves showed much deviation from normal, the irregularities falling into four main groups unassociated with the contemporary clinical and other biochemical manifestations.
5. The increase in the Ca. curve did not indicate the state of the CaO balance, and as in the control subjects, could not be associated with the urinary excretion.

- - - - - - - - - -

V.

Excretion of Calcium and Phosphorus in Nephritis.

A. Urinary Excretion: The question of excretion in nephritis falls next to be considered. Reference has already been made to the fact that for many years diminution in urinary excretion of calcium and phosphorus has been generally recognised. Marriott and Howland (30) were probably the pioneers in this respect when in 1916 they observed a decrease in urinary phosphorus in nephritis. In the following year Halveson Mohler and Bergeim showed a similar occurrence in respect of calcium.

Owing to the lack of balance studies, no comment seems to have been made on the elimination by bowel. In 1925 however, Hetenyi and Nogradi (15) published some observations on the behaviour of Ca. in nephritic subjects, and noted that there was an excessive amount of Ca. in the faeces. In order to avoid any difficulty arising from the question of absorption, they injected intravenously 10% solution of $CaCl_2$, and found that in uraemia the urine calcium output increased very slightly in the two hours following injection. Even in convalescent acute nephritis, the urinary excretion rose less than half the amount shown in normal subjects, showing that, whatever the cause of the impairment of renal excretion, some time elapsed before the latter recovered its power. No observations of faecal output during this procedure were recorded. They found that the low urinary calcium of nephritis was not increased when calcium was given by mouth, in marked contrast to the normal sequence of events. This failure to increase the Ca. content of the urine was most marked in cases of nephrosis.

In 1926, Boyd, Courtney, and McLachlan (4) also noted low urinary excretion of Ca., and concluded that the nephritic kidney was incapable of excreting this in normal fashion, as evidenced/

evidenced by the low total excretion and by the low concentration in the urine. With regard to phosphorus, they were of opinion that in nephritis urinary excretion of P. compared favourably with normal.

Scriver,(39) in 1928, recorded some observations on the excretion of calcium in two cases of nephrosis. He found low urinary Ca. and failed to obtain any increase after injections of parathyroid extract.

Thus, while all previous workers are unanimous on the subject of a low renal output of Ca. in nephritis, some doubt has been expressed as to the phosphorus diminution. In the present investigation eleven cases of nephritis were examined, four of them on two occasions, and the figures for urinary excretion show that, without doubt, the quantities of Ca. and P. voided by this route were abnormally small. Before discussing these in detail, it might be advisable to show the extent of the normal urinary output of these elements.

In 1920, Holt Courtney and Fales,(17) while studying the calcium metabolism of normal children, indicated that the main source of recovery of the surplus Ca. intake was the faeces. A year later, Findlay Paton and Sharpe(1) showed that the proportion of Ca. excreted by the urine is small, but increases with advancing age. Thus they found that, in children between 8 and 13 years, the urinary content amounted to between 7.3 and 9% of the intake; while between 17 and 44 years it represented 21 to 27%. Telfer,(42) in 1922, was of opinion that a great deal of the Ca. and P. intake is restricted to the gut, absorption being prevented by the formation of tri-calcium phosphate. He found that, in normal infants, the urinary Ca. was only a small fraction of the total excretion, while the P. amounted to 40% of the total phosphorus excreted. About the same time, Sherman and Hawley(40) reported a large number of Ca. and P. balance observations in healthy children of various ages.

A/

A series of their results was quoted by Boyd Courtney and McLachlan in 1926.(4) These show that, in children from 3–12 yrs. the urinary excretion of Ca. varied from 1.3 to 12.3 per cent of intake, averaging 4.9 per cent; whilst the P. ranged between 44 and 64 per cent of intake, giving an average of 51 per cent.

In a paper on mineral metabolism in coeliac disease, published in 1928, Telfer(43) reaffirmed his previous opinion that almost all the unutilised Ca. intake is recovered from the faeces in normal children. He indicated that the proportion of the P_2O_5 intake excreted by the urine depends on the condition of the intestinal contents, and that as a rule urinary and faecal contents of P_2O_5 are almost equal.

Macrae,(29) working in this laboratory, has found that in children of 2½–12 years the urinary output of Ca. represents on the average 6.74 per cent, and the P. 48.9 per cent of the respective amounts of Ca. and P. ingested. The three control subjects of the present series of balance investigations showed a similar distribution (Table XVI).

This method of expressing urinary excretion as a percentage of intake may seem peculiar, but it has been adopted wittingly, and for this reason. Suppose two children, A and B, given exactly equal amounts of Ca., and with exactly equal urinary outputs of Ca. If A has a greater retention than B, then the total output of A will be less than that of B, and the percentage of output appearing in A's urine will be accordingly greater, giving a fallacious idea of the urinary excretion. If the latter be expressed in terms of the intake, the equal urinary contents of A and B will then be seen to be equal. This is well illustrated by the following figures, taken from the present series of balances. In addition, the figures expressing "percentage of intake" show much greater proximity, and allow of easier comparison. Accordingly the results of other/

	CaO retent. in gms./Kilo/day.	Urinary CaO as % of Intake	Output	P_2O_5 retent. in gms./Kilo/day.	Urinary P_2O_5 as percentage of Intake	Output
C.H.	.087	7.6	17.5	.077	48.8	74.9
E.McL.	.037	7.1	9.37	.046	42.7	53.8

other workers have been, as far as possible, so expressed; and are presented in the table beneath.

Observer	Age of subject	% of CaO intake in urine	% of P_2O_5 intake in urine.
Findlay, Paton, Sharpe 1921	8-13 yrs.	7.3 - 9	-
Telfer 1922, 1928	Children	small amount	40-50
Sherman & Hawley 1922	3-12	1.3 - 12.3	44-64
Macrae 1929	2½-11	2.5 - 9	34-63
Control subjects of present series	6-7	4.7 - 7.6	33-49

It appears, then, that there is considerable variation in the urinary excretion, even in normal children. The average percentage of intake, calculated from this table, gives the normal urinary CaO as 6%: P_2O_5 as 50%, both these being approximate figures.

The figures for excretion in the nephritic subjects show very definite variation from these (Table XVII). The average amount of Ca. in the urine, for all 15 balances, whether in acute, convaslescent acute, or chronic forms of the disease, is 2.02% of the intake. The range of the nephritic urinary excretion is much less than in the normal figures quoted above. As will be seen from the table, the urinary CaO in a chronic case reached a maximum for the series of 3.9% of intake, well below the average figure of 6% in health. In no single instance of acute nephritis/

nephritis did the urinary calcium exceed 3% of intake, while in one subject it was found to be only 0.94%.

Of the four repeated balance observations (Table XVIII), there was apparent in three definite improvement in renal excretion of Ca. at the time of the second observation. The interval between the balance periods varied from three weeks to four months. In the other case, the first period was observed during tremendous diuresis which followed an attack of acute uraemia complicating a bronchiectasis. No satisfactory explanation could be found for the decreased excretion during the later balance period.

The behaviour of the urinary phosphorus was found to be roughly parallel to that of the calcium. From the average urinary content expressed in terms of the P. intake, it seems that the decrease is not so marked as in the case of Ca. (Table XIX) The average fraction of P. intake appearing in the urine, during the fifteen balance periods observed in subjects of nephritis, was 32% as compared with the normal average of 50%. Thus, while the Ca. showed only one third of its normal quantity, the P. was more than half the normal amount. Again it was noted that the range of urinary phosphorus content was smaller than in healthy children, being with one exception between 26 and 43% of intake. The lowest figure, 8.4% of intake, was shown by a case of chronic nephritis shortly before a fatal pericarditis. The maximum urinary excretion of phosphorus did not occur in that case which showed a maximum calcium excretion in the urine (Chart V). In fact, in all forms of nephritis there was apparent more defect in urinary Ca. than in P. although even the latter only approached the normal proportion in two instances, one of which was found in a convalescent child.

Here, as in the case of calcium, the four repeated balance observations showed that urinary excretion had improved in the interval. It was found that Case 5 which showed a decreased output/

output of Ca., had a slightly increased urinary P. demonstrating again that there is not absolute parallelism between the two.

As was indicated in the section on the calcium and phosphorus balances, no relationship could be traced between the retentions and the figures for urinary excretion (Charts III & IV: Tables XI, XIV). Likewise, the urine volume was not found to have any bearing on the quantitative excretion of Ca. or P. (Table XVII).

This is quite in accord with the observations of Wigglesworth and Woodrow,(45) who in 1924, found that in healthy adults after ingestion of large doses of phosphate, there was increased renal excretion. The latter was roughly parallel to the increase in blood inorganic P. but showed much greater variation, and was quite unrelated to the quantity of water excreted by the kidneys.

With one exception, previous references to the serum P. in nephritis have accepted the theory of "retention of phosphate" by the kidney. That there is some justification for this is shown when the serum and urinary phosphorus contents are compared (Chart IV). The lowest urinary P. of the present series occurred in case 4, who showed the highest serum level. The opposite state of affairs, however, does not maintain this reciprocal relationship, and this is more apparant when the four repeated balance studies are considered (Table XIX). Serum values within normal limits did not indicate a normal distribution of the P. excretion, and it is therefore fair to conclude that although a low urinary content of P. may occur coincidently with a high serum inorganic phosphorus, and although the two may have a common cause, yet they are not directly interdependent.

Looking at the urinary Ca. excretion from the same point of view, it is seen that in presence of the lowest serum value there is found the lowest excretion of Ca. (Chart III). But again, normal serum values do not foretell a normal urinary content of Ca. (Table XVIII), and it therefore seems that the latter is not directly dependent on the serum level.

These/

These observations on urinary excretion, then, may be briefly stated as follows:-

(1). In normal healthy children between 3 and 12 years of age, the portion of the intake of Ca. and P. excreted by the urine is fairly constant, and represents on the average 6% of Ca. and 50% of P. i.e. there is an approximate relationship of 1:8.

(2). In children of the same age, suffering from nephritis, the excretion of both Ca. and P. in the urine is reduced, the Ca. being affected to a greater degree. The average urinary content represents 2% of the Ca. and 32% of the P. intake, thus changing not only the quantities but also the relative proportion to a ratio of 1:16.

(3). As clinical recovery proceeds, the urinary excretion slowly improves.

(4). The amounts of Ca. and P. excreted in the urine of nephritic patients bear no relationship to their respective retentions, to urine volume, nor except indirectly to the serum levels for Ca. and inorganic P.

B. Faecal Output: Having considered the urinary output, there remains to be investigated the calcium and phosphorus recovered from the faeces. At the moment, the question of whether the faecal Ca. and P. is in part the result of excretion by bowel need not be discussed, and it is proposed to focus attention on the alterations found in these substances without regard to their previous metabolism.

In healthy children the distribution of the unutilised part of the Ca. and P. intake is fairly constant, varying of course in different individuals. From Sherman and Hawley's (40) figures, quoted above, it has been calculated that the faecal portion of the total phosphorus recovery averaged 37.7%. Macrae's (49) figures for normal children showed an average of 40%. in the faeces, of the total P rejected; while the control cases of the present series gave an average of 43.5% (Table XX). Thus/

Thus in 22 normal children, the faecal phosphorus amounted to, on the average, 39.2% of the total P. output. If this be expressed in terms of intake, it appears that 30.3% i.e. about one third of the ingested phosphorus is eliminated by the bowel.

When corresponding calculations are made for the nephritic balances, it is evident that 62.3% of the rejected P. is present in the faeces. There is therefore a relative increase in the faecal recovery. If this be expressed in terms of intake, it is found that an average of 54.2% i.e. more than half the ingested phosphorus appears in the faeces, showing that there is also an absolute increase in faecal content in nephritis.

A similar aberration from normal is evident in relation to the calcium recovery (Table XX). The average faecal content in healthy children was found to be 91% of the total output, representing 64.7% or almost two thirds of the Ca. intake. In nephritic subjects these figures are increased. A larger portion of the total output, averaging 97.4%, appears in the faeces, thereby accounting for 78.8% or more than three-quarters of the intake. Thus, an increase, relative and absolute, is found in both the Ca. and P. content of the faeces; but the increase in phosphorus is relatively the greater of the two.

This inequality is more easily appreciated if the ratio of CaO to P_2O_5 in the faeces be considered. In Macrea's normal children and in the control series of the present study considerably more CaO than P_2O_5 was present in the faeces. The ratio in these subjects averaged 1.34:1 (Table XX). When the nephritic figures are examined, it is found that the faecal CaO and P_2O_5 contents were more nearly equal, the average ratio being 1.08:1. That is, the ratio in nephritis is decreased.

If/

If, as has been suggested, the faecal content of Ca. and P. represents the amounts of these substances which have not been absorbed, i.e. if there is no re-excretion, it is difficult to see why the CaO/P_2O_5 ratio in nephritis should be uniformly decreased. It might be explained by a relatively poor absorption of P. the Ca. absorption remaining unaltered, but the evidence of both blood curves and urinary excretion is not in favour of such a theory.

During convalescence it might be anticipated that a decrease would be found in faecal CaO and P_2O_5, with an accompanying increase of CaO/P_2O_5 ratio, signifying a return to the normal distribution of the output. In the four repeated balances the interval between the observations varied from three weeks to four months. Only after the latter interval was definite evidence of such a return to normal found. In this subject, case 3, there was noted coincident fall in faecal content of Ca. and P., rise of CaO/P_2O_5 ratio, and increase in urinary excretion (Table XXI), the retantions remaining practically the same in both periods. When the balances were repeated after shorter intervals of 3, 4, and 6 weeks, the evidence of return to normal was much less marked. In each case the faecal CaO/P_2O_5 ratio had increased, and in two there was found improvement of the urinary Ca. excretion, while all three showed increased urinary P. excretion; but when the faecal elimination was examined, it appeared that there was actually an increase over that shown in the earlier period, with consequently reduction of the Ca. and P. retentions.

In two of the other balances (Cases 10,11) also observed in nephritic children during early convalescence, the distribution of the Ca. and P. recovery resembled that in the three cases quoted above. In each there was found a negative balance with an abnormally high faecal output, low urinary excretion, and low CaO/P_2O_5 ratio in the faeces. The significance of/

of this will become apparent when the question of intestinal excretion is discussed.

C. The Evidence of intestinal Excretion in Nephritis:

In view of the conclusion, arrived at from study of the blood curves, that in nephritis absorption is at least comparable with absorption of Ca. and P. in health, this demonstration of decreased urinary output with coincident increase in faecal content of Ca. and P. suggested the possibility of intestinal excretion. This is no new suggestion, since various observers have advanced it, with considerable supporting evidence, during the past few years. Earlier opinion was against such an occurrence. Telfer (42) in 1922 indicated that much of the ingested Ca. and P. was restricted to the gut, and that the amount of Ca. absorbed might be little more than the amount retained. He was of opinion that probably there was no re-excretion into the bowel. The question of intestinal excretion of P. was not considered.

In 1925 Greenwald and Gross (12), after injection into dogs of $CaCl_2$ and NaH_2PO_4, either separately or together, found increase in the excretion of both Ca. and P. by bowel and urine. The increase varied in amount but was roughly equal to the quantity injected, and was mainly recovered from the bowel.

Hunter and Aub (19), in 1926, while treating some cases of lead poisoning with parathyroid extract, observed an increased excretion of Ca., 80% of which appeared in the urine, the remainder in the faeces.

In the following year Percival and Stewart (34), working with cats, found that after intravenous injection of $CaCl_2$ there was little increase in urinary calcium; but obtained a large increase in the Ca. washed from an isolated loop of bowel. They concluded that the large intestine provides the main excretory route for Calcium.

In/

In addition to these observations, several references were found to excretion in renal disease. In 1925 Hetenyi and Nogradi (15) published some work on the behaviour of calcium in nephritis. They found that when Ca. was given by mouth to nephritic subjects, no increase in urinary excretion followed, and while there was no increased retention, the faecal calcium was in excess. In normal subjects this procedure led to increased urinary Ca. In order to avoid any uncertainty which might have been raised by the question of absorption, they injected intravenously 10% solution of $CaCl_2$ and found that normally there was induced an immediate increase in renal excretion of calcium, which continued for the remainder of the 2 hours' observation period. In convalescent acute nephritis the urinary output showed less than half the normal increase, while in uraemia any increase which occurred was negligible.

In 1928, Scriver (39) reported two cases of nephrosis treated with parathyroid extract, but could find no increase in urinary excretion of Ca. He observed that the Ca. content of the stool was high, and that it was increased by administration of parathyroid, attributing this to increased intestinal excretion following the increase in serum calcium produced by the extract.

Brain and Kay, (5) in 1929, stated that in some nephritic subjects, after intravenous injection of 0.55 gm. of phosphorus in the form of sodium glycerophosphate, no increase in urinary P. was obtained within two hours, in marked contrast to the minimum increase in normal subjects of at least 0.15 gm. In many other nephritic patients they found markedly low excretion of the injected P., so constantly present as to be a reliable test of renal function.

Thus both calcium and phosphurus when injected intravenously in nephritic subjects have failed to produce increase in renal output. This of itself is indicative of the presence of an

alternative/

alternative excretory route, which, as has been shown in dogs, cats, and human beings, actually exists in the intestinal tract. Whether or not, excretion is a normal function of the intestine in health is a point which has not as yet been decided. Bergeim's[1] work tends to show that phosphorus at least is both absorbed from and excreted into the intestine, and in rickets he found Ca. excretion also. Now, the distribution of the Ca. and P. recovery in rickets is very similar to that just described in nephritis, and at least one observer, Murdoch,[32] has noted that there is no gross defect in absorption of P. in rickets; therefore if Bergeim's suggestion of intestinal excretion is correct in the latter disease, there is no reason why it should not apply also to nephritis.

This question of intestinal excretion implies that the excess of Ca. and P. absorbed may be excreted by either the intestine or the kidney, the route depending on some controlling influence not at present understood. That this is probably correct is shown by the excretion in diabetes mellitus. Kahn and Kahn[24] in 1916 pointed out that the increased urinary excretion of calcium in this disease has been recognised since at least 1853. They noted a loss of Ca. with accompanying even greater loss of P. Nelson[33] in 1928 found that under comparable conditions, namely in subjects on ketogenic diet, there was excessive loss of calcium and phosphorus. Previously, on anti-ketogenic diet, these children showed adequate retention and normal distribution of the recovered Ca. and P. but while on ketogenic diet a shift of the major excretion from the stool to the urine took place, the increase in urinary Ca. being proportionately greater than the P. increase.

This is the exact opposite of what is found in nephritis, where the shift is from urine to faeces, again being more marked in the case of the calcium.

In/

In order to obtain some figures for this urinary type of excretion, two cases of diabetes mellitus (Cases 13,14) were observed during periods without and with insulin therapy. The diet, which remained unchanged throughout both periods, was so adjusted that during the non-insulin period considerable glycosuria was present. In the insulin period sufficient insulin was supplied to maintain a trace of sugar in the urine, so that the results might not be attributed to over dosage. In both children the retentions of Ca. and P. were definitely improved by the administration of insulin, the P. showing relatively greater increase (Table XXII).

The striking feature, however, of the glycosuric period was the urinary content of Ca. and P. particularly of the former (Table XXIII). In place of the normal content of about 6% of the Ca. intake, the urine in these diabetic children showed 46 and 31%, with marked fall under insulin treatment to 7.5 and 23% respectively. It thus appears that the kidney is capable of excreting many times its normal output of calcium when deprived of the influence, direct or indirect, of insulin. Unfortunately it was only possible to observe the blood Ca. curves in one child, but these showed increases of 2.7 and 2.0 mgs. per 100 ccs. of serum indicating that there was no great difference in absorption due to the presence or absence of an insulin supply (Table XXIV).

The redistribution of the phosphorus excretion was not quite so marked, but was very definite also. During the first period, without insulin, 80 and 60% of the P. intake appeared in the urine showing considerable increase over the normal average of 50%. When insulin was supplied the urinary P. output also fell, accounting for 39 and 58% of intake. Again blood curves are available for only one child. These showed increases of 1.5 and 2.4 mgs. per 100 ccs. of serum, indicating if anything better absorption during the insulin period i.e. during/

during the period of greater faecal output.

Thus, in this study there have been illustrated three different distributions of the calcium and phosphorus unutilised by the body. These are:-

(1) the distribution in normal children:

(2) the increased elimination by bowel in nephritis:

(3) increased urinary excretion in diabetes mellitus.

In none of these three groups was absorption shown to be far removed from normal; the retentions were found to be very much alike; and it was concluded that the difference in distribution of the recovery was due to alteration in excretion.

Intestinal excretion in nephritis: Acting on this hypothesis of an abnormal type of excretion in nephritis, and pursuing the suggestion that this takes place in the intestine, it seemed probable that if phosphorus was added directly to the circulating blood this abnormal excretion would reveal itself more markedly. Brain and Kay found that, in nephritis, intravenous injection of sodium glycerophosphate induced a subnormal increase, and in some instances no increase, in urinary P. within two hours. This observation suggests that either the increased urinary excretion in nephritis must be much more prolonged than in the normal, or that excretion is taking place by the only other possible route - the intestine. Accordingly, it was decided that, by means of a balance study, the distribution of the output should be determined in a suitable subject, and that subsequently, during a second balance period, intravenous glycerophosphate should be given. By this means it was expected that any extra intestinal excretion would become evident.

The choice of a subject was the first difficulty. It was essential that the renal damage should be severe and remain more or less unchanged for at least 15 days, i.e. for 3 pre-days, and two balance periods of six days each. Therefore, cases of acute/

acute nephritis could not be utilised, since the majority of such show definite improvement within a week of admission to hospital. A severe chronic nephritis seemed the ideal subject, but in children such a condition is by no means common.

The child, on whom the theory was ultimately put to the test, (Case 12), had suffered from chronic nephritis for several years. For some time after admission to hospital, all efforts to determine his retention failed because of vomiting, and when at last this was successful, his condition had improved considerably. He still showed albuminuria, amounting to one part Esbach, with some haematuria and the presence of occasional granular casts, but his N.P.N. had returned to a more normal level of 44.6 mgs.%. The diet consisted largely of fruit and vegetables, since milk seemed of itself to induce vomiting. The procedure was identical with that followed in the other balance studied, as were the methods of analysis. During the second period he was given intravenously an average of 8.5 ccs. of sodium glycerophosphate solution (approx. 12%) on each of the first five days, so that a period of 44 hours intervened between the last injection and the end of the balance period. This was planned to allow of all the injected P. being excreted. The phosphorus content of the injected solution was determined on several different samples.

During the first period low retentions of both CaO and P_2O_5 were found (Table XXV), which is not surprising when the low intake is considered. The distribution of the output was very much as in normal children and entirely different from that found in even convalescent acute nephritis (Table XXVII). Of the Ca. intake 12.8% was excreted by the urine, while the renal output of P. amounted to 57% of the phosphorus intake.

In the second period, when P. was given intravenously, the balances of both CaO and P_2O_5 became negative. The injected phosphorus was entirely excreted together with some additional P. and/

and was accompanied by increased excretion of calcium (Table XXVI). The urinary Ca. remained unchanged, but the P. content was increased, amounting to 78% of the intake - diet + injected phosphorus. There was increased faecal P. with at the same time increase in faecal Ca.

Greenwald and Gross (12) found that in dogs the amount of extra excretion after Ca. and P. injections varied, but advanced no explanation. None is apparent here either, since the urinary increase, amounting to 0.4382 gm. P_2O_5, more than compensated for the injected quantity of 0.29 gm P_2O_5.

From the point of view of its specific purpose, this investigation was a failure. The reasons for this have been in part presented above, namely the occurrence of clinical improvement before the balance could be determined, and the fact that a diet of low Ca. and P. content had to be employed. An additional reason became apparent only after analysis of the output during the first period, namely that the illness had been so far recovered from that a normal distribution of excretion was found. It was impossible to anticipate this, and therefore it is claimed that without further investigation, in view of the evidence previously discussed, the theory of intestinal excretion in nephritis need not be abandoned. Since it appears, from both nephritic and diabetic urinary contents, that the Ca. excretion is the more readily influenced, probably it would be better to concentrate future efforts on the excretion of calcium given intravenously. A further opportunity for such study has not been presented.

Two points brought out by the above investigation are, however, of vital importance. First of all it is clearly demonstrated that in man Ca. and P. excretion by the intestine can occur. The reason for the intestinal excretion of calcium in this instance is not at all obvious, and it can only be suggested that it occurred as a result of and possibly in/

in combination with the excreted phosphorus. Secondly, it appears that increased excretion in response to rise in blood content of P., is not accurately controlled, in this case over-compensating for the abnormal amount in the circulation with consequent production of a negative balance. This may be interpreted as another indication, the blood curves supplying the first one, that the control of phosphorus metabolism is not governed by a mechanism of extreme delicacy. It supports the inference, drawn from the excretion in various stages of nephritis, that adjustment of the rate of excretion is a lengthy process. Otherwise, why should an additional supply of P. over that which was shown to suffice for a retention, lead to the establishment of a negative balance? It has already been emphasised that the increase in urinary excretion alone was more than sufficient to account for the excess of phosphorus injected (Table XXVI), and even if the intestinal excretion be ignored, faulty regulation of excretion is apparent.

Likewise, the calcium-regulating mechanism cannot be well coordinated. In each period, precisely the same amount of Ca. was excreted by the urine in spite of the fact that during the second period there was increased Ca. loss by bowel. No attempt was made to compensate for this by a reduction of the urinary excretion, and it therefore must be concluded that urinary and intestinal excretions are not wholly interdependent, although they may give the impression of being so when larger quantities are under consideration as in the case of the balances in diabetes mellitus.

In light of this conclusion, that there is no close cooperation in activity between the two excretory channels, the kidney and the intestine, an explanation of the variation in the Ca. and P. balance observed in nephritic children becomes much/

much more feasible. If in acute nephritis it be granted that excretion by bowel occurs, possibly as a result of diminished urinary excretion, then with a somewhat dull regulating mechanism this intestinal activity would not be expected to decrease in proportion as the urinary output increased. Only when renal efficiency had improved to a considerable degree would there be diminution in intestinal excretion, so that in early convalescence the situation would be as follows. Excretion by bowel during the acute period must have been sufficient to maintain the normal balances of Ca. and P. found in this stage. When renal excretion began to improve, no compensatory fall in intestinal activity occurred; the balances were reduced, and provided a sufficiently rapid recovery of the kidney, negative balances were the inevitable result.

In three of the four repeated balances studies, in Cases 9, 5, and 8 the retentions and distribution of excretion closely agree with this conjecture (Table XXL). In the other two subjects in whom negative balances were found (Cases 10 & 11), this seems to have been the mode of their production. All five children were examined during early convalescence.

Still continuing the same idea, it might be expected that in late convalescence, when the regulating mechanism had been given time to effect the necessary adjustment in intestinal excretion, the retentions of Ca. and P. would have returned to a more normal level. The later period of Case 3, three months after the acute illness, shows this to be a correct forecast (Table XXI).

In the case of chronic nephritis with permanent renal inefficiency, the excretion would be anticipated mainly from the bowel, and of such magnitude that a normal retention would result. Cases 4 and 6 provide examples of this type of distribution. (Tables V & XVII).

Thus/

Thus the main factor in the determination of the balance would seem to be the time elapsing between the onset of clinical improvement and the date of the observation period. At present no suggestion can be advanced as to the mode of action of this regulator of excretion, since the action of the regulating mechanism in health is quite unknown. One point in regard to it seems however, from these nephritic observations, to be quite definite, that is lack of resiliency, a considerable stimulus being required to alter the main channel of excretion, and this having been accomplished, an equally great stimulus being required to induce a return to the normal distribution.

- - - - - - - - -

VI.

General Considerations.

In the introductory section of this paper it was indicated that previous workers found an acidotic condition in nephritis. For many years it has been recognised that the increase in serum inorganic phosphorus varies with the degree of acidosis, and that manifestations of the disease, other than acidosis, have little effect on the level of the inorganic P. The origin of this upset of acid-base equilibrium in renal disease has been attributed to three factors, retention of phosphorus, failure of the kidney to practise fixed base economy, and retention with possibly over-production of organic acids. The results of the present investigation alter this conception very considerably.

Salvesen (36), in a paper on "the serum electrolytes in renal disease", discussed the causation of this acidosis, and concluded that "phosphate retention" played a very minor part. This opinion was based on the observation that, after injection of large amounts of phosphate, no change in pH of the blood was noted, and he therefore laid more stress on the remaining factors, failure of the kidney to practise fixed base economy and retention of organic acids. Boyd, Courtney and McLachlan (4) suggested that "the evidence of phosphate retention given by blood and balance studies does not always agree", and the series of cases reported in this study shows definitely that in acute nephritis, in which the acidosis is generally found, there is no retention of phosphorus. It therefore seems that retention of P. must be abandoned as a causal factor, and it remains to show what light can be thrown on the question of excessive loss of fixed base.

In diabetes mellitus, and in children on ketogenic dietary treatment, there is definite acidosis which is accompanied by large increase in urinary output of calcium, and if the balance is negative the responsibility may justifiably be laid on

the kidney. The same cannot be said about nephritis, in which urinary excretion of Ca. is diminished. As the severity of the nephritis increases, the urinary calcium decreases i.e. as the acidosis becomes more severe, the urinary evidence of acidosis diminishes. No reference has been found to the occurrence of an acidosis during convalescence, yet in this stage of the illness the present study has shown that the renal activity is very similar to that found in the more acute phase. It has been shown that the retention of calcium is decreased during convalescence. In other words, there is "failure of fixed base economy" as regards Ca. during this period, but the kidney is not the main channel of excretion, and therefore it must be concluded that any such failure is not associated with nephritic acidosis. The other fixed bases, sodium and potassium, were not estimated, but so far as calcium is concerned the question seems to be definitely settled.

The position, then, is that nephritic acidosis may be due to excessive renal excretion of sodium and potassium combined with retention of organic acids. It is obvious that neither retention of P. nor excessive loss of Ca. play any part in the production of this acidosis, and from the decreased urinary output of these substances, during the period when acidosis, is commonly assumed to be most severe, it is evident that there must be very considerable fundamental differences between the reactions of the body to the acidosis of renal disease and the reactions in other conditions of upset of acid-base equilibrium.

Another point of importance emerging from this investigation is the parallelism exhibited by calcium and phosphorus. This is especially well shown by the graph of the balance studies (Chart II) in which retentions or losses of CaO and P_2O_5 were, almost/

almost invariably, approximately equal. This also is in direct opposition to previous opinion which, as has been frequently pointed out, affirmed retention of P. and loss of Ca. It is noteworthy that in the child who was given intravenous phosphate, when the P_2O_5 balance was reduced, an accompanying fall was observed in the CaO balance. The extra phosphorus was excreted by the kidney, the extra calcium by the intestine, so that increased retention or excretion of the one seems to demand a similar variation in the metabolism of the other. No exception to this general principle has been reported in any series of well-conducted balance observations, and although the significance of the relationship cannot be appreciated, it is surely more than a mere coincidence.

It is apparent, then, that the metabolism of calcium and phosphorus in nephritis suffers from considerable derangement, necessitating various adaptations, and is of a much more complex nature than has been indicated by previous investigations.

VII.
Summary.

(1) Blood serum. The observations of this study confirm those of previous workers, showing an increased serum inorganic phosphorus and decreased serum calcium in nephritis. In several cases the return of both to more normal levels is demonstrated by frequent estimations throughout the course of the illness, and the reverse is also illustrated by actual observations during the development of nephritis. The similarity of the variations in blood N.P.N. and serum inorganic P., and in blood CO_2 and serum Ca. is shown by means of graphs.

(2)/

(2) Balances. The results of Ca. and P. studies in eleven nephritic children are considered in detail, and contrasted with those in three control cases, and two cases of diabetes mellitus. The nephritic balances are positive and vary within normal limits except in the convalescent stage, in which decreased and negative balances are found. The retention is shown to be quite unconnected with the serum level, both as regards calcium and phosphorus, and to have no relation to the diminished urinary output. In all the balances determined, irrespective of whether there is retention or a negative balance, the CaO and P_2O_5 figures are approximately equal. It is therefore suggested that the theory of "retention" of phosphorus and deficiency of calcium is no longer tenable.

(3) Absorption. A.Phosphorus. A study of the absorption in normal and nephritic children by means of blood curves is reported, showing that phosphorus is well absorbed in nephritis. This conclusion is based on the observation that in twenty-two nephritic curves the average increase is comparable with that in nine control curves, and on the fact that neither the stage of the illness nor the presence of any particular manifestation of renal disease has a constant effect on the rate and extent of increase in the phosphorus curve. It is shown that the retention of P_2O_5 and the amount of P_2O_5 excreted by the urine are not dependent on the degree of activity of absorption as shown by the phosphorus curve.

B.Calcium. A similar investigation of absorption is considered in detail. The average increase in 26 serum calcium curves is exactly equal to the average increase in 9 normal curves, thereby showing that absorption is adequate. Considerable evidence is presented of upset of/

of the internal metabolism of Ca., giving rise to abnormal types of curve. These are classified according to their appearance when graphed as their significance has not been appreciated. There is no relationship between the absorption of Ca., assessed from the increase in the Ca. curve, and either the CaO balance or the urinary excretion of CaO.

(4) Excretion. The observations of previous workers, that there is diminished excretion of calcium and phosphorus in the urine of nephritic subjects, is confirmed; and the conclusion drawn that this is accounted for by impairment of renal function. The latter is shown to affect calcium to a much greater degree than phosphorus, thereby explaining the divergence of previous opinions as to impairment of phosphorus excretion.

It is clearly demonstrated that the decrease in urinary content of Ca. and P. is accompanied by relative and absolute increase in faecal content of both, and in view of the finding of satisfactory absorption of Ca. and P., the probability of compensatory intestinal excretion in nephritis is considered. By contrast of the normal distribution of excretion with that found in nephritis and in diabetes mellitus, presumptive evidence of an inter-changeability of the major part of the Ca. and P. excretion between kidney and intestine is obtained. An attempt to prove this theory of intestinal excretion in nephritis is described, and the reasons for its incomplete success are detailed. It is shown that excretion of calcium by bowel can certainly occur in convalescence, and an explanation is advanced of the low positive and negative balances found in this stage of the illness.

(5)/

(5) Acidosis. The accepted explanation of acidosis in renal disease is discussed in light of the results of this study. Retention of phosphorus and excessive loss of calcium are definitely discredited as causal factors, and it is shown that the reaction of the body to nephritic acidosis differs materially from the reaction to other forms of acidotic disturbance.

———oOo———

BIBLIOGRAPHY.

1. Bergeim, O.; Journ.Biol.Chem. Vol.70, 29, 1926.

2. Bauer, W., & Ropes, M.W.; Journ.Amer.Med.Assoon. Vol.87,1902 1926 Chicago.

3. Blum, L., Aubel, E., Hansknecht, R.; Bull et mem Soc.med.d'hop. de Paris 54,1561,1925 Abbrev.Journ.Amer.Med.Assoc. Vol.78,467 1925.

4. Boyd, G.L., Courtney, A.M., McLachlan, I.F.; Amer.Journ.Dis. Child. Vol.32, 29, 1926.

5. Brain, R.T., Kay, H.D.; Quart.Journ.Med. Vol.22, 203, 1929.

6. Byrom, F.B., Kay, H.D.; Brit.Journ.Exp.Path. Vol.8, 240, 1927.

7. Denis, W., Minot, A.S.; Arch.Int.Med. Vol.26, 99, 1920, J.B.Ch. 55, 183.

8. Denis W., Hobson, S.; Journ.Amer.Med.Assoc. Vol.80,1175,1923

9. De Wesselow, O.L.V.; Quart.Journ.Med. Vol.16, 341, 1923.

10. Fetter, W.J.; Arch.Int.Med. Vol.31, 412, 1923.

11. Findlay, L., Paton, D.N., Sharpe, J.S.; Quart.Journ.Med. Vol.14 352, 1921.

12. Greenwald, I., Gross, J.; Journ.Biol.Chem. Vol.66, 201, 1925.

13. Halverson, J.O., Mohler, H.K., Bergeim, O.; ibid Vol.32, 171 1917.

14. Hartmann, A., Darrow,D; Journ.Clin.Invest. Vol.VI, No.1,1928.

15. Hetenyi, G., Nogradi, S.; Klinische Woche, Vol.4 1308 1925.

16. Hjort, A.M.; Journ.Biol.Chem. Vol.65, 782, 1925.

17. Holt, L.E., Courtney, A.M., Fales, H.L.; Amer.Journ.Dis.Child. Vol.19, 97 and 201, 1920.

18. Howland, J., Kramer, B.; Amer.Journ.Dis.Child. Vol.22 105 1921.

19. Hunter, D., Aub, J.C.; Quart.Journ.Med. Vol.20, 123, 1926-27.

20. Jansen, W.H.; Journ.Amer.Med.Assoc. Vol.83, 1959, 1924.

21. Jones, M.R., Nye, L.L.; Journ.Biol.Chem. Vol.47, 321, 1921.

22. Kahn, B.S., Roe, J.H.; Journ.Amer.Med.Assoc. Vol.86, 1761,1926.

23. Kahn, B.S., Roe, J.H.; ibid. Vol.88, 981, 1927.

24. Kahn, M., Kahn, M.H.; Arch.Int.Med. Vol.18, 212, 1916.

25. Kramer, B., Tisdall, F.F.; Journ.Biol.Chem. Vol.47, 475, 1921.

26. Kramer, B., Tisdall, F.F.; ibid. Vol.56, 439, 1923.

27. Kramer, B., Tisdall, F.F., Howland, J.; Amer.Journ.Dis.Child. Vol.22, 560, 1921.

28. Leicher, H., J.A.M.A., 80, 882, 1923.

29. Macrae, O.C.H.C., personal communication.

30. Marriott, W.McK., Howland, J.; Arch.Int.Med. Vol.18, 708, 1916.

31. Mason, E.H.; Journ.Biol.Chem., Vol.47, 3, 1921.

32. Murdoch, G.; Arch.Dis.Child. Vol.2, No.2, 1927.

33. Nelson, M.V.K.; Amer.Journ.Dis.Child. Vol.36, 716, 1928.

34. Percival, G.H., Stewart, C.P.; Quart.Journ.Med. Bol.19, 235, 1926.

35. Rockwood, R., Burrier, C.W.; Arch.Int.Med. Vol.33, 643, 1924.

36. Salvesen, H.A.; Acta Med.Scandinav. Vol.69, 126, 1928.

37. Salvesen, H.A., Hastings, A.B., McIntosh, J.F.; Journ.Biol Chem. Vol.60, 311 and 327, 1924.

38. Salvesen, H.A., Linder, G.C.; ibid. Vol.58, 617 and 635, 1923.

39. Scriver, W.de M.; Journ.Clin.Investig. Vol.VI, 115, 1928.

40. Sherman, H.C., Hawley, E.; Journ.Biol.Chem. Vol.53,375,1922.

41. Steenbock, H., Hart, E.B.; Sell, M.T., Jones, J.H.; ibid. Vol.56, 375, 1923.

42. Telfer, S.V.; Quart.Journ.Med. Vol.16, 45 and 63, 1922.

43. Telfer, S.V.; Glasgow Med.Journ. April 1928.

44. Tisdall, F.F.; Journ.Biol.Chem. 50, 329, 1922.

45. Wigglesworth, V.B., Woodrow, C.E., Proc.Roy.Soc. B.95 558, 1924.

46. Wills, L.; Brit.Med.Journ. Vol.1, 302, 1925.

47. Wills, L., Sandeson, P., Paterson, D.; Arch.Dis.Child. Vol.1, 245, 1926.

———————oOo———————

Table I.

Control series of observations in children convalescent from illnesses other than nephritis.

Condition	Age in years.	Serum Ca. in mgs. per	Serum P. 100 ccs.
Alopecia areata	14	10.04	5.4
Rheumatism	12	-	5
Alopecia areata	11	9.95	4.28
" "	10	9.1	2.66
Chorea	10	9.91	4.75
Rheumatism	10	9.6	5
Melena	10	9.62	4.61
Banti's disease	10	10.8	3.22
		10.35	3
Fröhlich's syndrome	9	10.22	5.33
Rheumatism	9	9.76	5.71
"	9	8.9	5.33
Alopecia areata	8	9.65	4.8
" "	8	-	6
Ileo-colitis	8	9.71	6.31
Rheumatism	7	10.9	4.7
Alopecia areata	7	11.4	5
Purpura	6	10	4.61
Chorea	6	10.38	4.8
Average		10.01	4.75

Table II.

Serial observations of serum Ca. and inorganic P in nephritis.

	Age in years	Serum Ca. in mgs.	Serum P. per 100ccs.	Clinical Notes.
Acute nephritis	12 3/12	11.9	4.13	on admission
		10.34	6	1 wk. later
		10.46	5.21	4 months later.
		10.85	5	5 " " - well.
Acute nephritis	11	8.88	4	on admission
		9	6.66	2 weeks later
		8.65	5.85	5 " " improving
Acute nephritis convalescent	11	9.56	3.2	
		9.43	4.28	
		10.54	5.71	well.
Uraemia	9	8.54	4.89	1 dy. after convulsions.
		9.86	5.1	almost well.
Acute nephritis	8½	9.3	5.2	on admission
		9.21	4	2 weeks later
		11.6	4.6	3 " "
		11.6	5.45	7 " " almost well
Acute nephritis	8	7.91	5.66	oedema ++
		9.27	5.15	3 weeks later.
Acute nephritis	7	9.77	5.45	
		9.6	5.21	
Acute nephritis	6½	8.07	5.33	? slight oedema
		10.17	4.44	10 days later
		-	4.7	15 " "
		10.8	4.51	4 weeks later - well.
Renal dwarfism	6½	10.19	-	
		11.06	4.6	8 weeks later.
Acute nephritis	6	10.61	4.89	on admission
		9.64	4.8	2 weeks later
		10.31	4.8	2½ " "
		-	5	4 " "
		9.77	4	7 " "
		9.81	5	11 " " - well
Acute nephritis	6	7.76	4.7	
		9.28	6.15	2½ weeks later.
		-	5.45	6 " "
Acute nephritis	6	7.66	5.45	on admission
		9.33	6	1 week later
		8.57	6	4 " " - relapse
Acute nephritis	5	9.95	6	oedema +++
		9.11	7.06	2 dys. later: less oedema
		9.74	4.8	4 weeks " - well.
Acute nephritis convalescent	4	9.91	6	
		9.41	-	5 weeks later
		9.81	4.8	9 " "
Acute nephritis		7.2	-	oedema +++
		8.49	4.21	" 1 week later
		8.25	5.3	2 " "

Table III.

Two cases showing the increase of serum Ca. and decrease of serum inorganic P. during recovery from a severe attack of nephritis.

Subject	Age in years.	Ser.Ca. Mgs. %	Ser.P. Mgs.%	Blood* N.P.N.	Blood* CO_2	Notes.
Case 5 Acute nephritis	8	7.79	4.4	97	54.3	Acute uraemia – convulsions
		9.64	4.8	92	51.1	½ day later – improved
		7.87	6	71	46.9	1 " " "
		7.87	3.58	67	49.4	2 " " convulsions again
		8.14	3.87	60	52.6	3 " " " stopped.
		8.91	4.8	43	50.9	7 " " improving
		9.61	5	41	52.5	2 weeks " "
		9.24	4.8	50	54.5	7 " " almost well
		10.22	5.71	47	–	9 " " well.
Case 12 Chronic nephritis.	12	6.3	10	53.6	55.6	very ill: vomiting.
		–	8.57	–	–	1 day later
		4.53	13.3	113.2	45.9	10 days " I.S.2.
		4.35	12	193.5	30.1	13 " "
		4.8	–	–	–	16 " " F.P.(A.B.C.)
		4.08	11.54	113.3	37.8	18 " "
		4.62	10	84.4	33.5	25 " "
		7.55	7.5	62.1	–	6 weeks " much improved
		9	5.58	59.1	51	7½ " "
		9.4	6.1	46.2	52.5	10 " "
		9.24	6.15	44.6	55.8	12 " " fairly well
		9.4	4.9			25 " " well: albuminuria.

* I am indebted to Dr. Morris for these figures on blood N.P.N. and CO_2.

Table IV

Showing decrease in serum Ca. and increase in serum inorganic P during development of renal disease.

	Age in years	Ser.Ca. mgs. %	Ser.P. mgs.%	Blood* N.P.N.	Blood* CO_2	Notes.
Case 4 Chronic nephritis	13	7.64	12	153	44.5	very ill: oedema ++
		5.6	–	342.8	30.6	1 day later: worse
		3.74	16	353	46.5	11 days " : 3 days before death.
M.W. Cardiac decompensation	8	9.08	4	–	–	no albuminuria
		10.87	4.52	–	–	2 weeks later: much better
		9.48	5	–	–	4 " " oedema & albuminuria
		7.26	2.07	–	–	9 wks. later oedema & albuminuria: very ill.
B.McL Purpura	6	10	4.61	–	–	haematuria gone.
		9.72	4.28	–	–	developed albuminuria
		8.57	6	–	–	I.S.2.

NEPHRITIC BALANCE FIGURES. TABLE V.

SUBJECT.	CASE 1.	CASE 2.	CASE 3.		CASE 4.	CASE5.		CASE 6.	CASE 7.	CASE 8.		CASE 9.		CASE 10.	CASE 11
Age in years.	8	6	12.$\frac{3}{12}$	12.$\frac{7}{12}$	13	8	8.$\frac{1}{12}$	6½	10.	6	6.$\frac{5}{52}$	5.	5.$\frac{3}{52}$	6½	8½
Wt. in Kilos.	26	16.4	26	27.4	25.	26.4	24.4	11.6	22.6	18.8	17.54	15.	14.8	13.8	20.
Duration of Expt. in days	6	6	7	6	4	6	6	7	5	5	6	6	6	5	7
Diet (Milk-c.cs	600	420	600	500	300	210	280	240	400	280	280	260	260	210	360
Diet (Sugar-gms	12	8	-	4	8	-	-	-	8	4	4	-	-	12	-
	5x	5x	5x	5x	6x	7x	5x	6x	5x	5x	5x	5x	5x	5x	5x
CaO Intake.	4.65	3.234	4.8	3.84	2.7	2.293	2.212	2.232	3.06	2.1	2.15	1.95	2.13	1.575	2.79
" in urine	0.044	0.039	.087	.136	.021	.063	.038	.088	.041	.048	.073	.022	.0575	.046	.03
" in faeces	2.61	2.277	3.29	2.41	1.58	1.14	1.62	1.74	2.46	1.58	2.308	1.8778	2.0965	1.53	3.101
" Total Output	2.654	2.316	3.377	2.546	1.601	1.203	1.658	1.828	2.501	1.628	2.381	1.8998	2.154	1.576	3.131
" BALANCE per kilo per day	+ .077	+ .057	+ .054	+ .048	+ .044	+ .042	+ .023	+ .035	+ .025	+ .025	- .013	+ .0033	- .0017	- .00007	- .017
P_2O_5 Intake	6.54	4.536	6.6	5.67	3.78	3.216	2.884	3.08	4.36	2.52	3.18	2.73	2.86	2.1	3.96
" Urine	2.45	1.69	1.84	1.92	.32	1.02	.938	.82	1.87	.764	1.197	.9146	1.2177	.81	1.1

NEPHRITIC BALANCE FIGURES (CONTD.)

SUBJECT.	CASE 1.	CASE 2.	Case 3.		CASE 4.	CASE 5.		CASE 6.	CASE 7.	CASE 8.		CASE 9.		CASE 10.	CASE 11.
P_2O_5 In Faeces	1.575	1.75	3.24	2.31	2.11	1.212	1.597	1.827	2.038	1.44	1.977	1.803	1.98	1.49	3.18
" Total Output	4.025	3.44	5.04	4.23	2.43	2.232	2.535	2.647	3.908	2.204	2.174	2.7176	3.1977	2.3	4.28
" Balance per kilo per day	+.096	+.068	+.058	+.053	+.054	+.038	+.014	+.039	+.02	+.017	+.0003	+.00083	-.225	-.014	-.016
Faecl Weight.	20.47	20.9	16.2	12.1	17.7	6.43	10.6	11.35	12.4	9.8	10.87	16.35	14.575	10.96	15.88
Urine Vol. in C.cs.	1,881	1,573	2,033	1,750	692	2,750	903	956	1,176	1,826	1,019	800	960	1,517	1,181

TABLE VI

SUBJECT.	CONTROL CASES. 15.	16.	17.	C.1.	C.2.	Dr. Macrae's Normal Cases. G.	McN.	F.	D.	M.	Control Balance. Figures.
Age in Years.	7.	6.	6.	9.	9.6/52.	11.	2.6/12.	5.	11¼	10.	
Weight in Kilos.	21.36.	20.	15.	27.	28.46.	26.32.	12.	14.08.	21.5	30.	
Duration of expt. in days.	6.	6.	6.	7.	7.	7.	6.	6.	6.	7.	
DIET (Milk ces.	400.	380.	300.	-	-	-	-	-	-	-	
DIET (Sugar	-	-	-								
DIET (-	5x	5x	5x								
CaO - Intake.	3.1	2.87	2.325	2.4	2.74	2.88	2.	2.4	2.8	2.8	
" in urine.	.2362	.135	.166	.0603	.217	.201	.179	.147	.172	.255	
" in faeces	1.115	1.89	1.603	.94	2.1404	1.3583	1.321	1.709	1.79	1.5656	
" total output.	1.3512	2.025	1.769	1.0003	2.3574	1.5593	1.5	1.856	1.962	1.8206	
" balance per kilo per day	+ .081	+ .042	+ .037	+ .052	+ .018	+ .0508	+ .042	+ .039	+ .039	+ .033	
P_2O_5 - intake	4.4	3.83	3.3	3.3	3.96	3.96	2.75	3.3	3.85	3.85	
" in urine	2.147	1.26	1.408	1.718	1.352	1.65	1.536	1.798	2.44	1.586	
" in faeces	.717	1.82	1.205	.83	2.06	.974	.792	1.138	1.057	1.3753	
" total output	2.864	3.08	2.613	2.548	3.412	2.624	2.328	2.936	3.497	2.9613	
" Balance per kilo per day	+ .071	+ .037	+ .046	+ .028	+ .019	+ .0514	+ .035	+ .026	+ .016	+ .0296	
Faecal wt. per day	6.25	7.935	9,75	5.2	12.1	8.93	12.01	9.1	12.43	8.75	
Urine Vol. in c.cs.	1,502	1,207	1,128	886	1,207	1,270	800	970	1,283	1,300	

Table VII

Subject	Ser. Ca. in mgs. per 100 ccs	CaO retent. in gms. per kilo per day.	Ser. Inorg. P. in mgs. per 100 ccs.	PO_4 retemt. in gms. per kilo per day.	Bl. N.P.N In mgs. per 100ccs	Bl. Cl. in mgs per 100ccs	Oedema.
Case 1	9	+.077	6.66	+.096	45.4	325	-
Case 2	7.76	+.057	4.7	+.068	67	360	-
Case 3	10.34	+.054	6	+.058	43	320	-
	10.46	+.048	5.21	+.053	50	320	-
Case 4	5.82	+.044	12	+.054	343	410	++
Case 5	8.14	+.042	3.87	+.038	60	370	+
	9.24	+.023	4.8	+.014	50	320	-
Case 6	10.19	+.035	4.6	+.039	86	365	-
Case 7	9.91	+.025	6	+.02	46	300	-
Case 8	10.61	+.025	4.89	+.017	57	350	±
	9.77	-.013	4	+.0003	48	340	-
Case 9	9.21	+.0033	7.06	+.00083	37.5	320	±
	9.74	-.0017	4.8	-.0225			-
Case 10	8.07	-.00007	5.33	-.014	36	320	±
Case 11	9.71	-.017	4	-.016	46	280	-

Table VIII.

Subject	Age	Condition	Inorg, P. in mgs./100ccs serum after NaH_2PO_4 gms. IV Before	1 hr.	2 hrs	4 hrs	Max. Inc.	Clinical Notes
Case 16	6	Chorea	4.8	8	7.7	6.6	3.2	well
R.C.	12	Chorea	5	7.06	6.48	6	2.06	well
J.F.	9	Chorea	5.33	7.06	6.41	5.85	1.73	well
J.S.	10	Melena	4.61	5.71	5.85	5.33	1.24	well
Case 15	7	Ileo-colitis	6.31	8.16	6.86	6.66	1.85	well
Case 17	6	Bronchitis	5.85	8	8.57	7.4	2.72	convalescent
G.P.	7	Rheumatism	4.7	5.45	5.1	5.02	0.75	well
A.S.	10	"	5	5.48	6.31	-	1.31	well
J.R.	9	"	5.71	7.06	6.31	-	1.35	well.

Table IX.

Subject	Age in years.	Condition	P. in mgs. per 10^0 ccs. serum after NaH_2PO_4 gms. IV. Before	1 hr	2 hrs	4 hrs	5 hrs	7 hrs	9-10 hrs	13-14 hrs
G.P.	7	Rheumatism	4.7	5.45	5.1	5.02	-	5.2	5.6	-
A.S.	10	" "	5	5.48	6.31	-	-	-	-	5.21
J.R.	9	" "	5.71	7.06	6.31	-	-	-	-	5.77
M.W.	8	Cardiac "	5	6.31	6.66	5.85	-	5.45	-	-
Case 14	6¾	Diabetes Mellitus	4.61	6.66	6.85	7.06	-	5		

Table XI

Arranged in order of the increase in P. curve

Subject	Increase in curve mgs. inorg. P./100 ccs. serum.	P_2O_5 retention gms. per kilo per day	% of P_2O_5 intake excreted by urine.
Case 8 (1st period)	2.65	+.0003	37.6
Case 1	2.6	+.096	37.5
Case 3 (2nd period)	2.3	+.053	33.8
Case 8 (1st ")	2.05	+.017	30.3
Case 3 (1st ")	2	+.058	27.8
Case 9 (1st ")	1.8	+.0008	33.6
" (2nd ")	1.7	-.0225	42.5
Case 5 (2nd ")	1.65	+.014	32.5
Case 7	1.05	+.02	42.9
Case 11	0.7	-.016	27.7
Case 4	0.65	+.054	8.4

SUBJECT.	Age in years	Condition.	Inorg. P. in mgs per 100 ccs. serum. after NaH_2PO_4 gms. iv. Before	1 hr.	2 hrs.	4 hrs.	Max. Iner.	CLINICAL NOTES.
W.H.	8.4/12	Ac. Neph.	4.28	5.45	5.58	5.1	1.3	Convalescent.
Case 7	10.11/12	do	6	7.06	7.06	6.66	1.06	do
E.M.	7.1/12	do	5.21	6.81	7.31	6.15	2.1	Early convalescent.
Case 11	8.4/12	do	4.6	4.7	5.3	5.	0.7	Convalescent.
J.W.	9.4/12	do	8.57	12	10.8	8.9	3.43	In acute stage.
Case 1	11.10/12	do	6.66	9.23	8	6.85	2.57	Convalescent.
Case 5	9.4/12	do	4.8	5.71	6.48	5.71	1.68	do
Case 4	13.8/12	Ch. Neph.	12	12.63	12.63	12.63	0.63	Very ill : died two weeks later.
D.B.	5.1/12	Ac. "	4.9	6.15	5.71	6.	1.25	Great Oedema, generalised.
Case 12	11.7/12	Chr. "	12	13.33	13.33	13.33	1.33	Very severe nephritis: did not appear ill.
			9.23	10.	10.	9.6	0.77	Much improved - 2 weeks later.
			6.15	7.27	7.27	7.27	1.12	Almost well: 2months later.
Case 3	12.3/12	Ac. "	6.	8.	7.5	6.3	2.	In acute stage.
	12.8/12		5.21	7.5	7.06	6	2.29	Convalescent: 5 months afterwards.
Case 8	6.4/12	do	5.	6.31	7.06	6.31	2.06	In early convalescence.
	6.5/12		4.	6.66	5.21	4.44	2.66	One month later.
Case 9	5.1/12	do	7.06	8.88	8	8.27	1.82	Acute stage: much oedema.
	5.2/12		4.8	6.48	6.48	5.6	1.68	Apparently well: one month later.
J.D.	9.	do	4.89	6.	6.48	6.31	1.59	Just after uraemic convulsions.
			5.1	6.	6.	5.6	0.9	One month later: well.
E.M.	8.	do	5.66	6.	6.31	5.85	0.65	Acute stage: much oedema.
			5.15	6.85	7.5	6.85	2.35	Oedema gone: N.P.N. still over 60 mgs % Urine, I.S.2 Seems quite well.

TABLE X

Table XII.

Subject	Age in years.	Condition	Serum Ca. in mgs. per 100 ccs after Ca. Lact. gms. IV Before	2 hrs	4 hrs	6 hrs.	Incr.	Clinical Notes
Case 16	6	Chorea	10.38	11.41	11.5	10.72	1.03	well
J.F.	9	Rheumatism	8.9	10	9.24	9.08	1.1	well
J.S.	10	"	9.62	10.95	10.1	10.05	1.33	well
Case 15	7	Ileo-colitis	9.71	10.1	10.2	10	0.49	well
Case 17	6	Bronchitis	9.62	11.05	10.3	10.1	1.43	convalescent
A.S.	10	Rheumatism	9.6	10.14	9.86	9.77	0.54	well
J.R.	9	"	9.76	10.7	9.86	9.86	0.94	well

Table XIV

Subject	Increase in Serum Ca. curve in mgs./100ccs	CaO retention in gms./kilo per day	% of CaO intake excreted by urine.
Case 6	2.87	+ .035	3.9
Case 11	2.5	-.017	1.07
Case 7	1.39	+ .025	1.34
Case 3 1st period	1.36	+ .054	1.8
Case 5 2nd period	1.07	+ .023	1.7
Case 1	1.04	+ .077	0.94
Case 8 2nd period	1.0	-.013	3.25
Case 5 1st period	0.89	+ .042	2.7
Case 9 1st period	0.7	+ .0033	1.13
2nd "	0.52	-.0017	2.68
Case 3 2nd period	0.5	+ .048	3.5
Case 8 1st period	0.36	+ .025	2.3
Case 4	0.22	+ .044	0.8

TABLE XIII

SUBJECT.	AGE IN YEARS.	CONDITION	Serum Ca. in mgs.per 100 c.cs. Before	after Ca. 2 hrs.	4 hrs.	6 hrs.	Max. Iner.	CLINICAL NOTES.
J. McG.	1½	Chronic Nephritis	10.96	13.07	11.14	10.52	2.11	Oedema
W.H,	8.4/12	Acute "	9.43	11.82	9.74	10.08	2.39	Late Convalescence.
Case 7.	10.11/12	" "	9.91	10.7	11.3	12.17	2.26	Early do.
			9.41	10.49	9.86	10.22	1.08	5 Weeks later: still albuminuria.
E.M.	7.1/12	" "	9.6	10.76	10.17	9.43	1.16	1 Week after uraemic twitching & Oedema.
Case 3.	12.3/12	" "	10.34	11.7	10.73	9.9	1.36	Acute Nephritis - improving
			10.46	10.96	9.95	10.39	0.5	4/12 later - almost well.
Case 11.	8.4/12	" "	11.6	14.1	12.3	10.3	2.5	Late Convalescence.
Case 8.	6.4/12	" "	9.64	10.	9.28	8.92	0.36	Early do
			9.77	10.77	9.41	9.23	1.0	Late do
Case 12.	11.7/12	Chronic Nephritis	4.8	4.9	5.0	6.57	1.77	Very ill but did not appear so F.P.(A.B.C.
			4.62	5.0	4.88	5.15	0.53	I.S.Q. 10 days later.

TABLE XIII (contd.)

SUBJECT	AGE IN	CONDITION	Serum Ca. in mgs. per 100 c.cs. Before	after Ca. 2 hrs.	4 hrs.	6 hrs.	Max. Iner.	CLINICAL NOTES.
Case 12. Contd.	11.7/12	Chronic Nephritis	9.24	9.86	9.9	9.52	0.66	2/12 later: much better: Esbach still 1 part.
J.W.	9.4/12	Acute "	8.7	9.58	8.27	9.35	0.88	Some Oedema.
Case 6.	6½	Chr. "	11.06	13.93	10.8	9.5	2.87	Renal Dwarfism.
Case 5.	9.4/12	Acute "	7.87	8.76	7.34	7.87	0.89	Uraemia - ? Conscious: Some Oedema.
			8.91	9.9	9.45	9.18	0.99	Some Albuminuria: ten days later.
			9.24	10.31	-	9.76	1.07	do two months later.
Case 1.	11.10/12	" "	9.0	10.04	9.7	9.24	1.04	Early Convalescence.
Case 4.	13.8/12	Chr. "	5.82	6.04	5.91	5.42	0.22	Extremely ill: fair amount of Oedema.
D. B.	5.1/12	Acute "	6.97	7.6	7.29	8.88	1.91	Tremendous Oedema.
Case 9.	5.1/12	" "	9.16	9.72	9.86	9.35	0.7	Oedema.
			9.74	10.26	9.74	9.58	0.52	Well.
J.D.	9.	" "	8.54	8.54	8.77	8.77	0.23	1 Day after Uraemic Convulsions: no Oedema.
			9.86	10.45	9.4	9.68	0.59	Well.
E.M.	8.	" "	7.91	8.91	8.7	8.26	1.0	Much Oedema.
			9.27	9.56	9.58	9.0	0.31	Oedema gone: N.P.N.&c. still high: 2 weeks later.

Table XV

Subject	Increase in Serum Ca. curve in mgs./100ccs	CaO retention in gms./kilo per day	% of CaO intake - excreted by urine
Case 15	0.5	.087	7.6
Case 16	1.03	.042	4.7
Case 17	1.43	.037	7.1

Table XVI - Controls

Subject	Intake of CaO gms per day	Output of CaO in urine in gms per day	Output of CaO in urine as % of intake	Intake of P_2O_5 in gms./day	Output of P_2O_5 in urine in gms per day	Output of P_2O_5 in urine as % of intake	Urine vol. in ccs./day
Case 15	3.1	.2362	7.6	4.4	2.147	48.8	1,502
Case 16	2.87	.135	4.7	3.83	1.26	33	1,207
Case 17	2.325	.166	7.1	3.3	1.408	42.7	1,128
C. 1	2.4	.0603	2.5	3.3	1.718	52.07	886
C. 2	2.74	.217	7.5	3.96	1.352	34.1	1,207
G.	2.88	.201	6.9	3.96	1.65	41.6	1,270
McN.	2	.179	8.96	2.75	1.536	55.8	800
F.	2.4	.147	6.1	3.3	1.798	54.5	970
D.	2.8	.172	6.1	3.85	2.44	63.03	1,283
M.	2.8	.255	9.1	3.85	1.586	41.2	1,300
Average			6.656			46.68	

Table XVII

Nephritics

Subject	Intake of CaO gms. per day	Output of CaO in urine in gms per day	Output of CaO in urine as % of intake	Intake of P_2O_5 in gms/day	Output of P_2O_5 in urine in gms per day	Output of P_2O_5 in urine as % of intake	Urine vol. in ccs/day
Case 1	4.65	.044	,94	6.54	2.45	37.5	1,881
Case 2	3.234	.039	1.2	4.536	1.69	37.2	1,573
Case 3 I.	4.8	.087	1.8	6.6	1.84	27.8	2,033
" 2.	3.84	.136	3.5	5.67	1.92	33.8	1,750
Case 4	2.7	.021	.8	3.78	.32	8.4	692
Case 5 I.	2.293	.063	2.7	3.216	1.02	31.7	2,750
2.	2.212	.038	1.7	2.884	.938	32.5	903
Case 6	2.232	.088	3.9	3.08	.82	26.6	956
Case 7	3.06	.041	1.34	4.36	1.87	42.9	1,176
Case 8 I.	2.1	.048	2.3	2.52	.764	30.3	1,826
2.	2.15	.073	3.25	3.18	1.197	37.6	1,019
Case 9 I.	1.95	.022	1.13	2.73	.9146	33.6	800
2.	2.13	.0575	2.68	2.86	1.2177	42.5	690
Case 10	1.575	.046	2.92	2.1	.81	38.1	1,517
Case 11	2.79	.03	1.07	3.96	1.1	27.7	1,181
Average			2.02			32.0	

Table XVIII

Case No.	1st Period Urine CaO as % of intake.	1st Period Ser.Ca. mgs./100ccs	2nd Period Urine CaO as % of intake.	2nd Period Ser.Ca. mgs./100ccs.	Notes
3	1.8	10.3	3.5	10.4	Acute nephritis with slow convalescence
8	2.3	10.6	3.25	9.9	Acute nephritis.
5	2.7	8.1	1.7	9.3	Uraemia: diuresis during 1st period.
9	1.13	9.1	2.68	9.7	Acute nephritis.

Table XIX

Case No.	1st Period. Urine P_2O_5 as % of intake	1st Period. Ser.inorg.P. in mgs/100ccs	2nd Period. Urine P_2O_5 as % of intake.	2nd Period. Ser.inorg.P. in mgs"100ccs	Notes.
3	27.8	6.0	33.8	5.2	As in Table XVIII.
8	30.3	5.1	37.6	4.0	
5	31.7	4.0	32.5	4.8	
9	33.6	7.1	42.5	4.8	

Table XX.

	No. of observ.	Faecal CaO as % of intake	Faecal CaO as % of output	Faecal P_2O_5 as % of intake	Faecal P_2O_5 as % of output	Faecal CaO / Faecal P_2O_5
Sherman & Hawley	12	69.2	92.2	28.2	37.7	-
Macrae	7	60.3	89.9	32.6	40	-
Control cases of present series.	3	56.9	86.9	33.4	43.5	-
Average in normal Children	22	64.7	91	30.3	39.2	1.34
Average in nephritic Children.	15	78.8	97.4	54.2	62.3	1.08

Table XXI.

Subject	Faec. CaO as % of intake	Urine CaO as % of intake		Faec. P_2O_5 as % of intake.	Urine P_2O_5 as % of intake.		Faec. CaO / Faec. P_2O_5
Case 3 Acute stg.	68.5	1.8	.054*	49.1	27.8	.058+	1.01
4 mths. later; late convales-ence.	62.7	3.5	.048*	40.7	33.8	.053+	1.04
Case 5 Acute stg.	49.6	2.7	.042*	37.7	31.7	.038+	0.94
1 mth. later Convales-cent.	73.2	1.7	.023*	55.3	32.5	.014+	1.01
Case 8 Acute stg.	75.2	2.3	+.025*	57.1	30.3	.017+	1.10
5 wks. later Convales-cent.	107.3	3.25	-.013*	62.1	37.6	.0003+	1.17
Case 9 Acute stg.	96.3	1.13	+.0033*	66.0	33.6	+.0008+	1.04
3 wks. later Convales-cent.	98.4	2.68	-.0017*	69.2	42.5	-.0225+	1.06

*CaO retention per Kilo per Day.

+P_2O_5 retention in gms. per Kilo per Day.

Table XXII

	Case 13		Case 14	
	No insulin	Insulin	No insulin	Insulin.
Age in years	10	20 units am.& pm.	8	12 units am.& pm.
Weight in Kilos	23.5		19.6	
Duration of balance period days.	5	5	6	6
Diet	Milk 900ccs. Butter 2ozs. Diabetic Roll 50gms.		Milk 1100ccs Butter 2ozs Diabetic Roll 50gms.	
CaO-intake gms.	1.46	1.363	1.647	1.625
-urine "	.67	.103	.52	.381
-faeces "	.42	.701	.61	.385
-total output "	1.09	.804	1.13	.766
-Balance p.K.p.D "	+ .016	+ .024	+ .026	+ .044
P_2O_5-intake gms.	2.26	2.133	2.526	2.617
-urine "	1.8	.84	1.53	1.51
-faeces "	.48	.73	.65	.325
-total output "	2.28	1.57	2.18	1.835
-Balance p.K.p.D "	- .00085	+ .024	+ .017	+ .039
Faecal weight"	4.56	5.68	5.15	3.7
Urine Vol.ccs.	1,130	700	1,215	1,047
Urine sugar gms.%	5.9	trace	1.9	trace.

Table XXIII

Subject	Intake of CaO in gms per day	Urine CaO as % intake	Urine CaO as % output	Intake of P_2O_5 in gms/day.	Urine P_2O_5 as % intake	Urine P_2O_5 as % output	Urine vol. in ccs/d
Case 13 No insulin	1.46	45.9	61.4	2.26	79.6	79	1130
20 units am.& pm.	1.363	7.5	12.8	2.133	39.3	53.5	700
Case 14 No insulin	1.647	31.5	46	2.526	60.5	70.1	1215
12 units am.& pm.	1.625	23.3	49.7	2.617	57.7	62	1047

Table XXIV

		No insulin	Insulin
		mgs.per 10	ccs ser.
Case 14	Serum P. before NaH_2PO_4 gms.IV orally –	4.52	4.61
	" 1 hr.after " –	5.2	6.66
	" 2 hrs " " –	6.0	6.85
	" 4 hrs " " –	5.85	7.06
		Mgs.per 10	0ccs ser.
	Serum Ca.before Ca.Lactate gms.IV orally –	7.47	9.56
	" 2 hrs after " –	8.95	11.56
	" 4 hrs " " –	10.17	10.43
	" 6 hrs " " –	9.21	10.34

Table XXV

Case 12	Control Period	Period during which sodium glycerophos. injected
Age in Years	12	12
Weight in Kilos	30	30
Duration of expt.--days.	6	6
Diet	low protein, high carbohydrate content	
P_2O_5 injected intraven./day		0.293 gms.
CaO--daily intake in gms.	.3823	.3823
- " in urine " "	.0493	.0487
- " " faeces " "	.318	.453
-total recovery	.3673	.5017
-balance /K./day	+ .0005	- .004
P_2O_5--daily intake in gms.	.9772	1.2705
- " in urine " "	.557	.9952
- " " faeces " "	.293	.336
-total recovery	.85	1.3312
-balance /K/day	+ .0042	- .002
Daily Faecal weight (gms)	11.37	15.61
" urine volume (ccs)	1,244	1,155

Table XXVI

Case12	CaO Intake in gms./day.	CaO Output in gms/day Urine	Faeces	Total	P_2O_5 Intake in gms./day.	P_2O_5 Output in gms/day urine	Faeces	Total.
First Period	.3823	.0493	.318	.3673	.9772	.557	.293	.85
Second Period	.3823	.0487	.453	.5017	1.2705	.9952	.336	1.3312
Increase	-	-	.135	.1344	.2933	.4382	.043	.4812

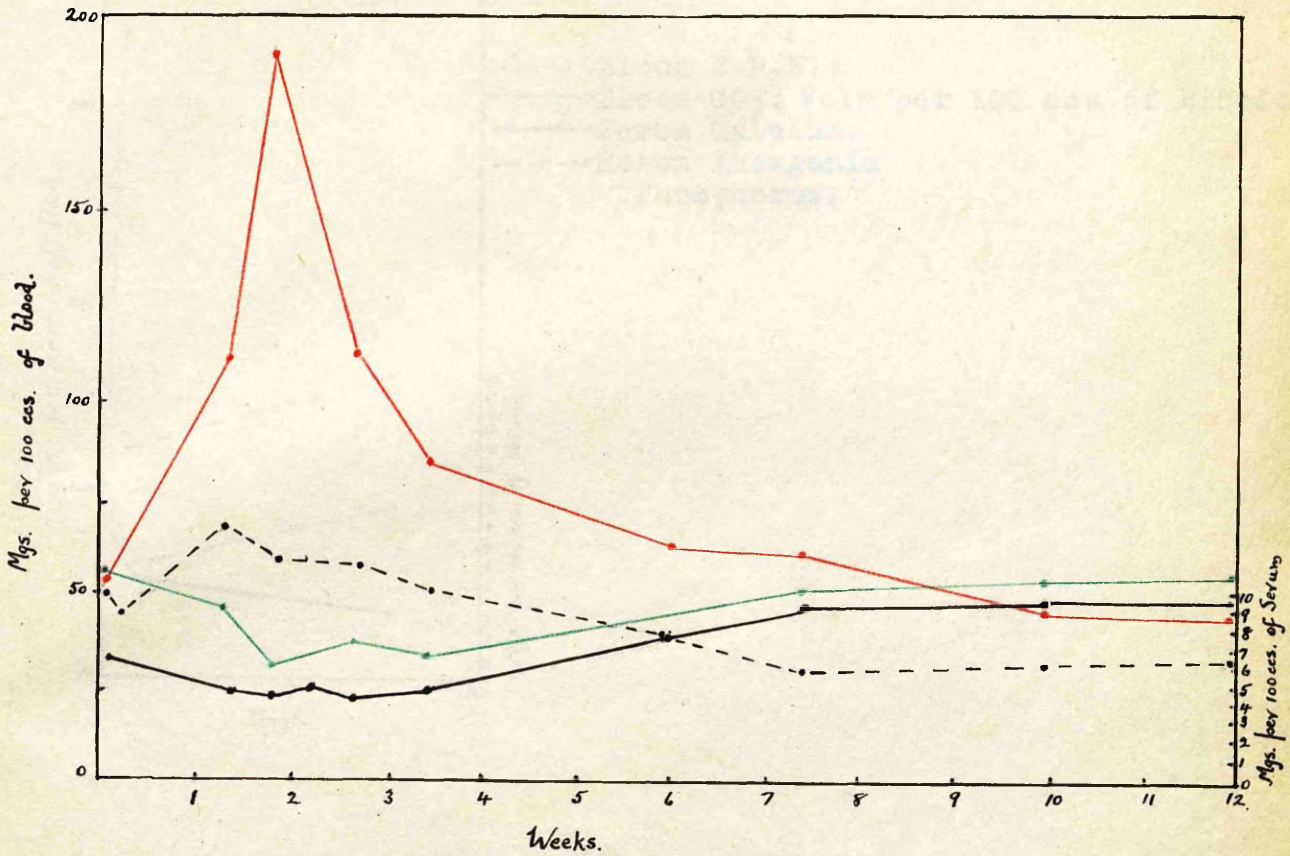
Analysis in quadruplicate.

Table XXVII

Case 12	Urine Content: % of intake CaO	P_2O_5	Faecal Content: % of intake CaO	P_2O_5	CaO P_2O_5
First Period	12.8	57.01	83.2	57.0	1.08
Second Period	12.8	78.3	118.4	78.3	1.34

———oOo———

Chart IA. figures taken from Table III. Case 12.



Blood N.P.N.:
Blood CO_2: Vols per 100 ccs of Blood
Serum Calcium:
Serum Inorganic Phosphorus:

Chart IB. figures taken from Table III. Case 5.

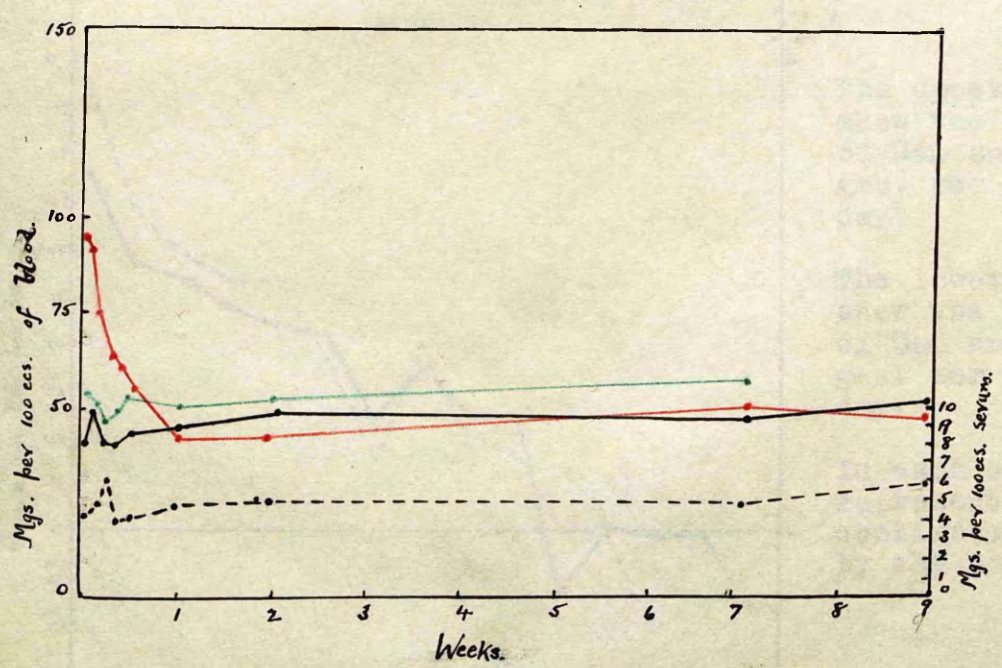


Chart III. figures taken from Table V.

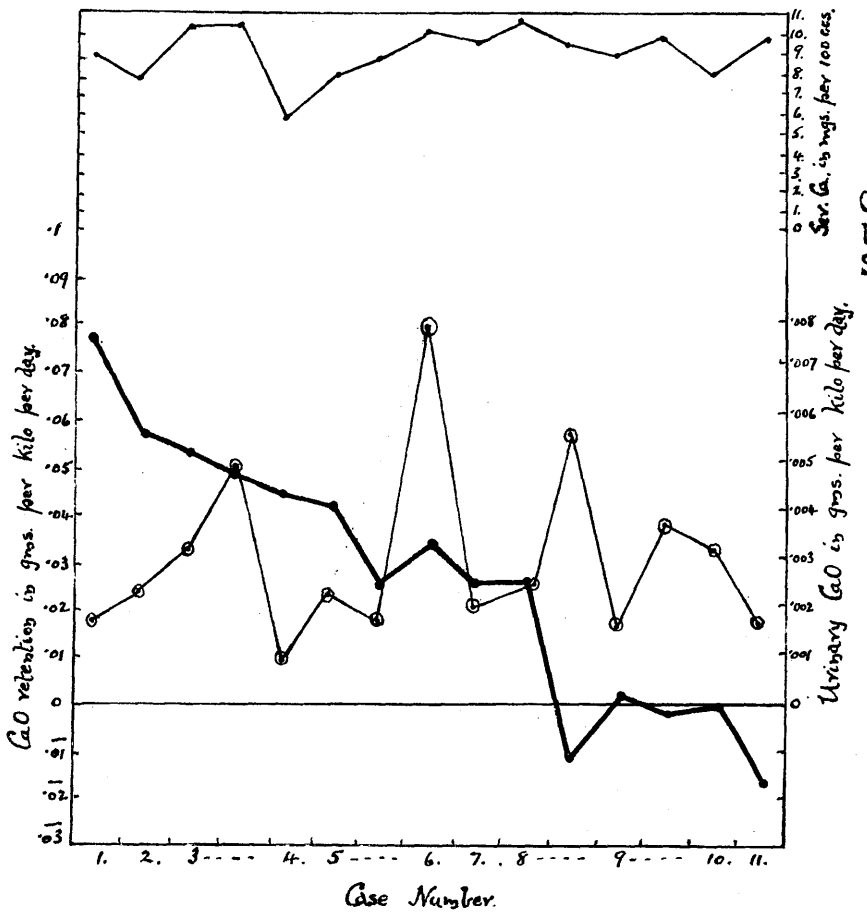
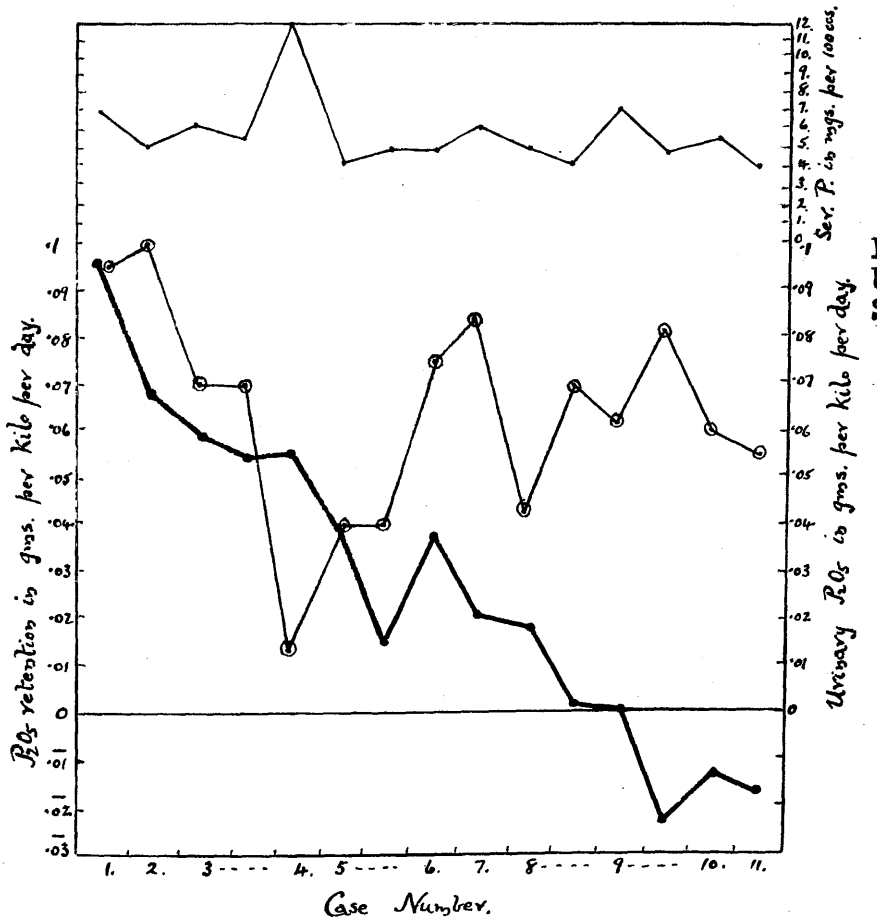


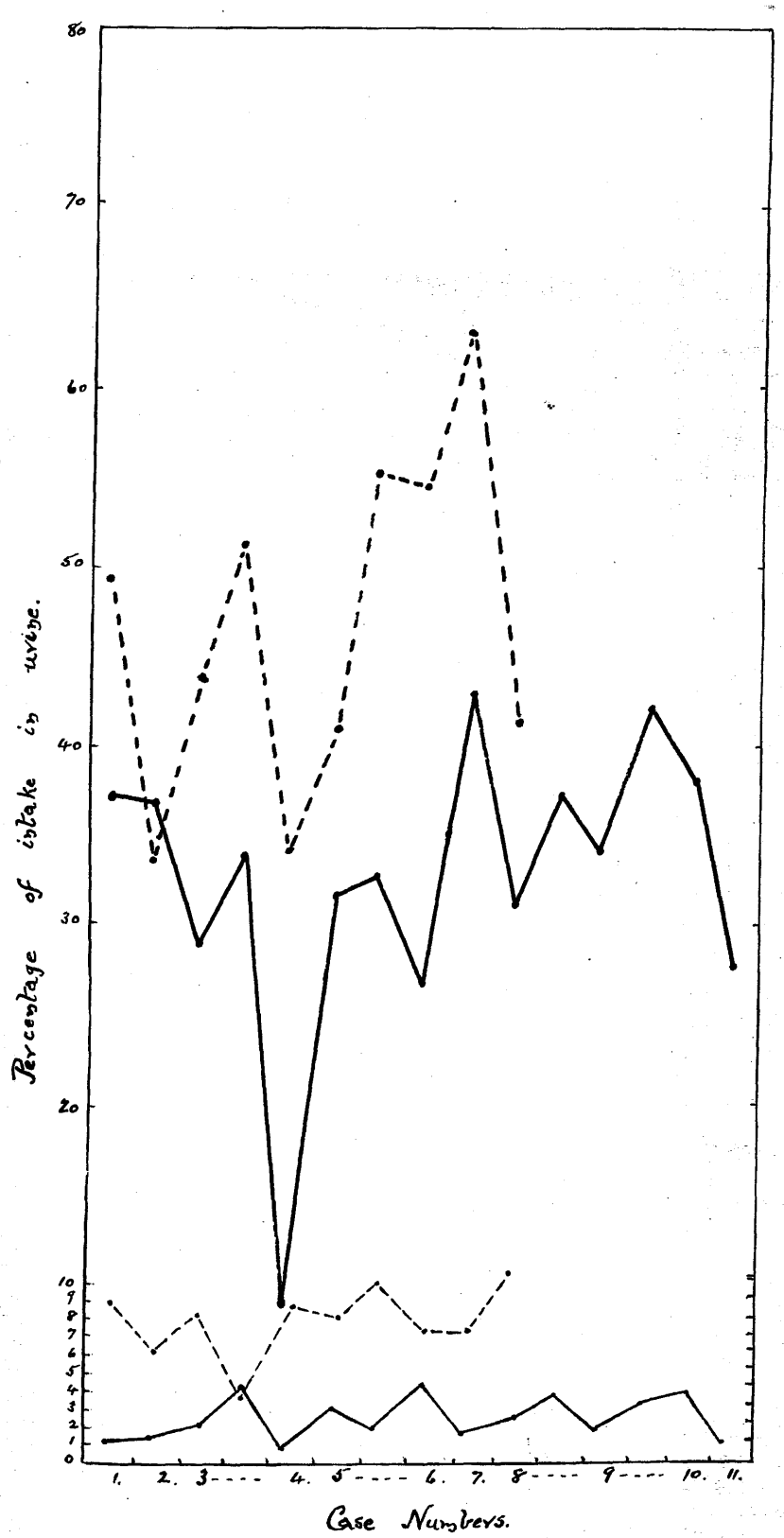
Chart IV. figures taken from Table V.



Percentage of Total Excretion of Calcium and Phosphorus found in Urine.

Chart V. figures taken from Tables V & VI.

Heavy continuous line – nephritic P_2O_5 figures
Heavy dotted line – control P_2O_5 figures
Light continuous line – nephritic CaO figures
Light dotted line – control CaO figures
} urinary excretion



Charts showing Serum Phosphorus Curves in Control Cases.
figures taken from Table VIII.

Chart VI

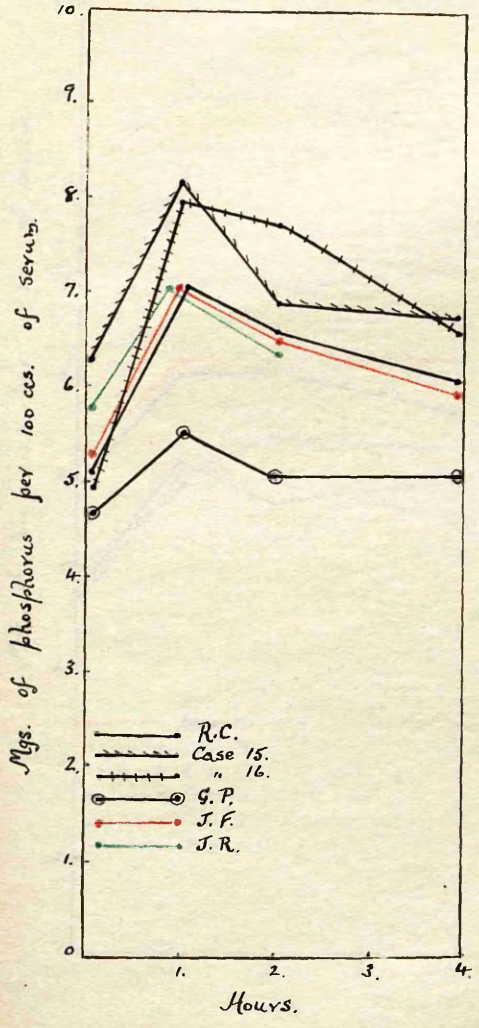


Chart VII

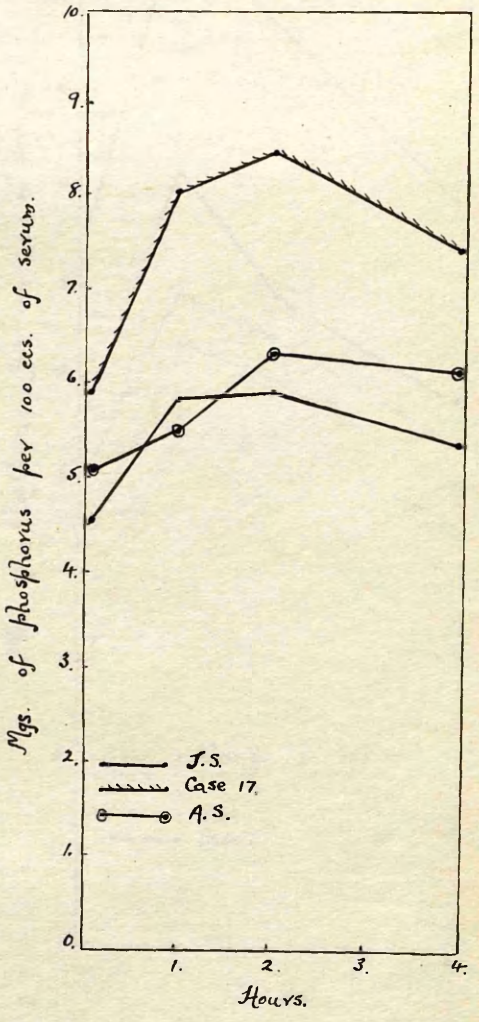
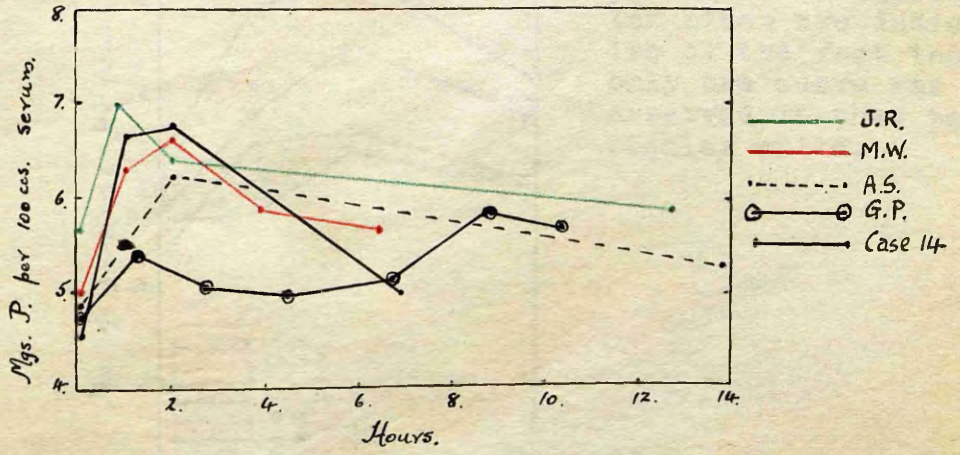


Chart VIII. Prolonged phosphorus curves.
figures taken from Table IX



Charts showing Serum Phosphorus Curves in Nephritis.
figures taken from Table X

Chart IX.

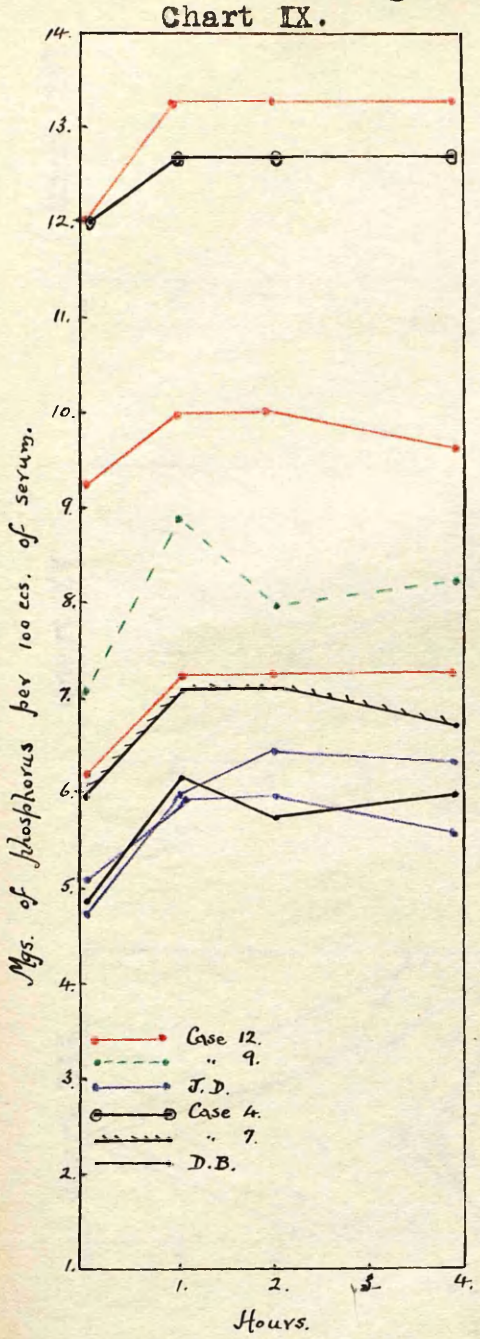


Chart X.

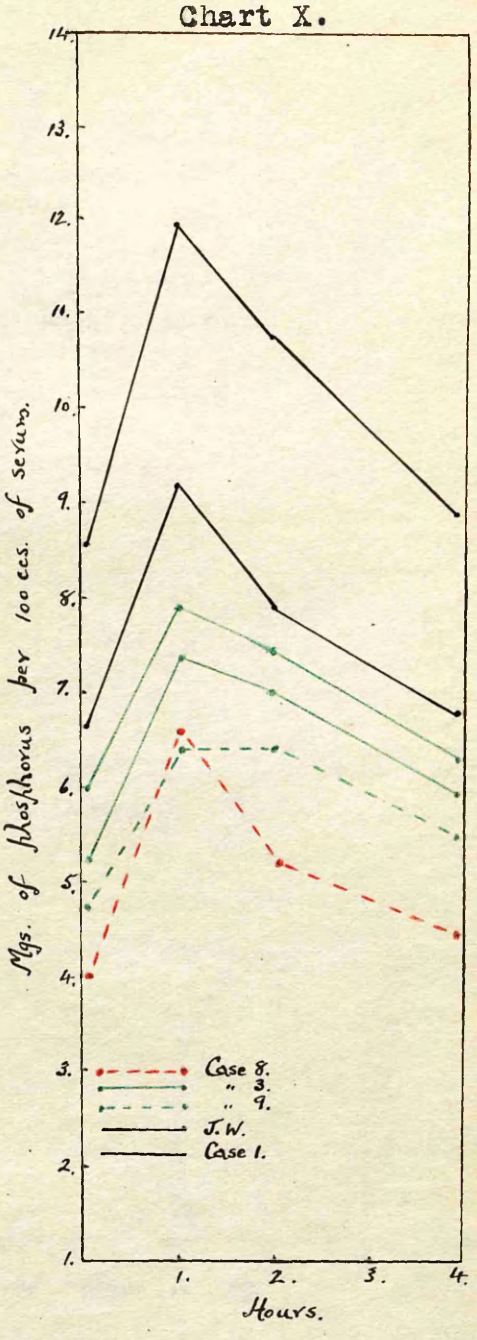
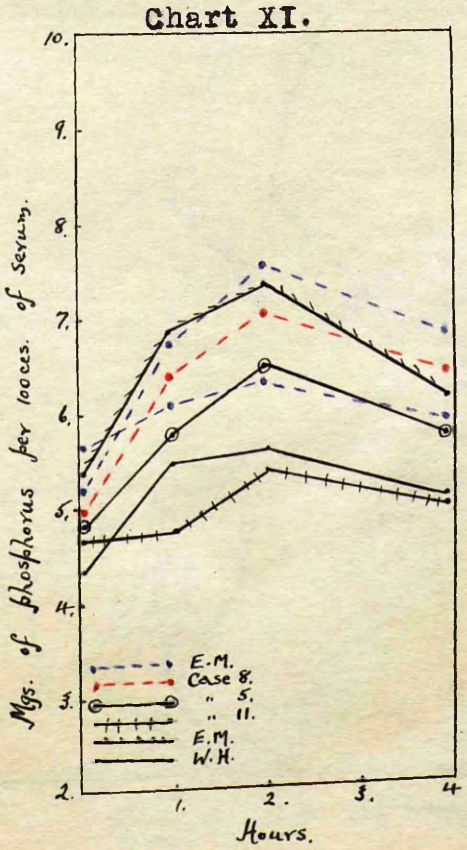
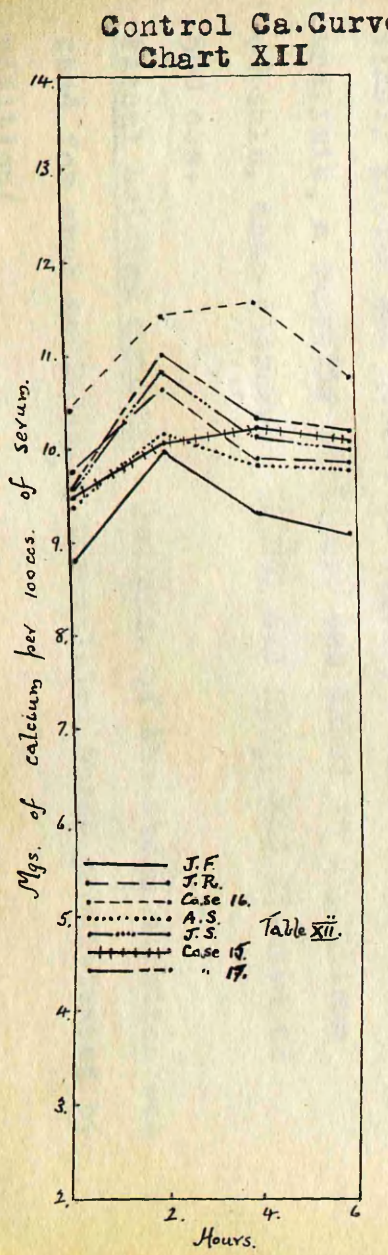


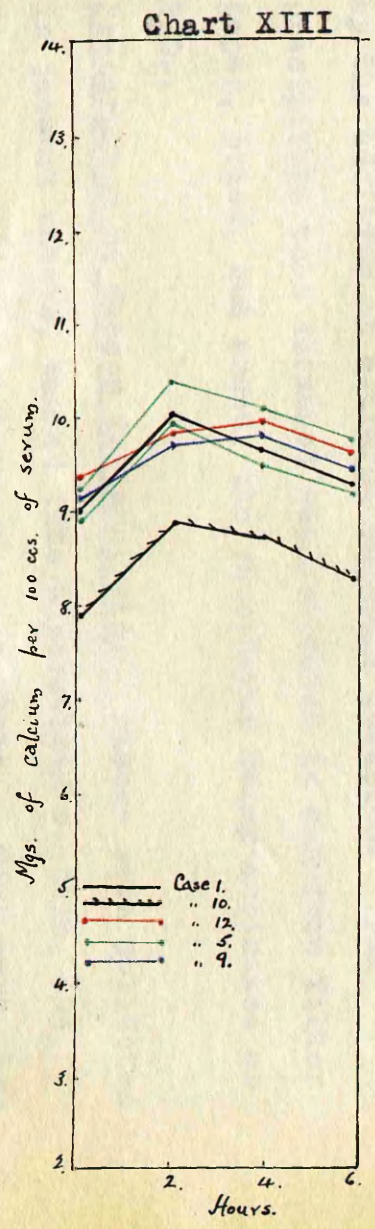
Chart XI.

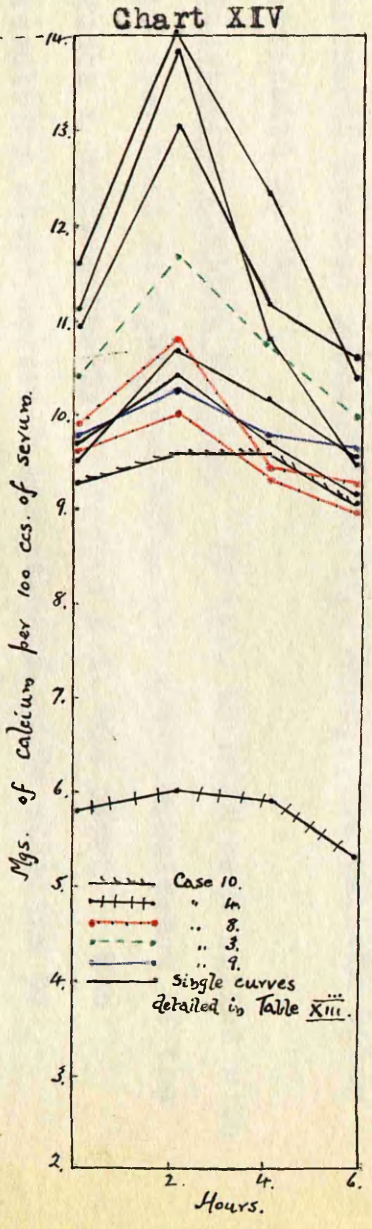


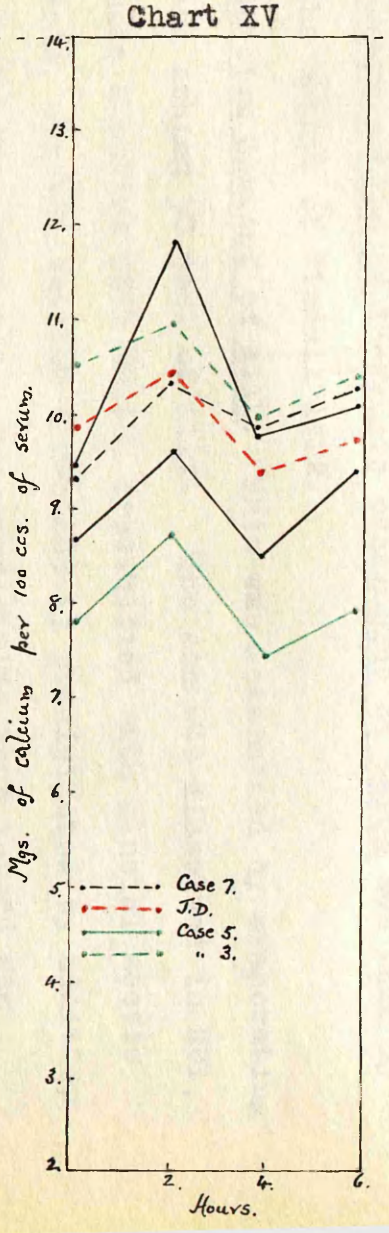
In Charts IX, X & XI repeated curves in one subject are represented in colours. Ink lines are indicative of the fact that only one curve was observed in that particular child.

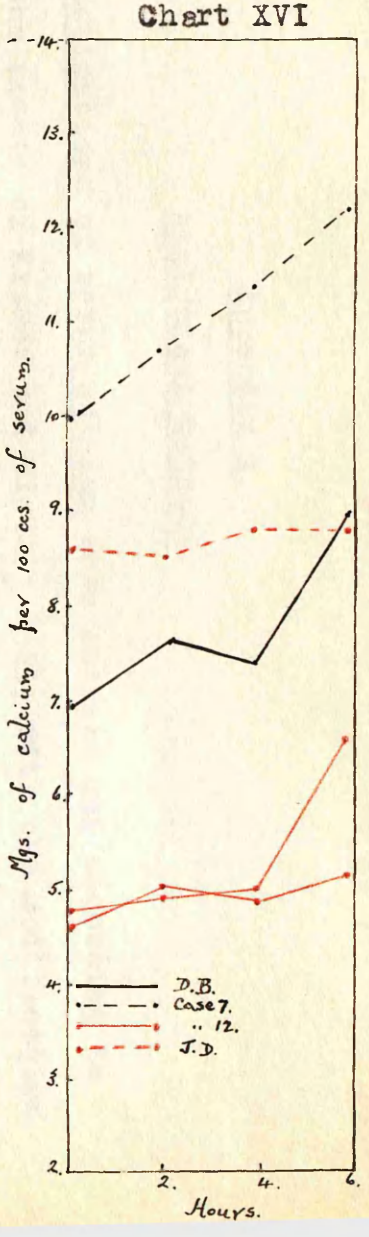
Serum Calcium Curves in Nephritic Subjects – figures taken from Table XIII.











Appendix I.

Analytical Methods.

1. Estimations of serum calcium were carried out according to the method of Kramer and Tisdall[25] 1921, with the modification suggested by the authors in 1923.[26]

2. Determination of inorganic phosphorus of serum was made by the method of Tisdall[44] 1922.

3. Calcium content of milk. This was determined by evaporating and ashing 50 ccs. of milk. The ash was dissolved in HCl, made alkaline with NH_4OH, reacidified with glacial acetic acid, and the calcium subsequently precipitated by addition of ammonium oxalate. The precipitate thus formed was filtered through ash-free paper, dissolved in H_2SO_4, and titrated against standardised $^N/_{10}$ $KMnO_4$, the calcium being estimated as CaO.

4. Phosphorus content of milk. 20 ccs. of milk were boiled with 10 ccs. each of H_2SO_4 and HNO_3, and after subsidence of the fumes a small quantity of copper foil was added. The resulting clear solution was diluted, made alkaline by addition of NH_4OH, reacidified with HCl, and further treated by the addition of citrated magnesia solution. The precipitate thus obtained was collected in ash-free filter paper, dried, and ashed, the phosphorus being estimated as P_2O_5.

5. Preparation of faeces for analysis. Faeces were collected in jacanet sheets, washed into a porcelain capsule, and dried to constant weight on the hot plate. They were then finely ground and stored in tightly stoppered bottles. For analysis, a quantity of 5 gms. was ashed in a platinum capsule, then dissolved in HCl and HNO_3, and diluted to 500 ccs.

Faecal calcium content. 100 ccs. of the above solution was used for each estimation, the calcium being precipitated by addition/

addition of ammonium oxalate exactly as in determination of of milk calcium content.

Faecal phosphorus content. 100 ccs. of the above solution was employed, made alkaline by addition of NH_4OH, and subsequently treated by the method described for estimation of phosphorus in milk.

6. Urine. The urine for each 24 hours of the balance period was collected under toluol, measured etc., and a measured quantity retained. At the end of each period, the retained fractions were well mixed and used for analysis.

Urinary calcium content. 250 ccs. of urine were boiled with potassium persulphate and HCl, filtered, made alkaline with NH_4OH, reacidified by addition of glacial acetic acid, and treated as in the case of milk analysis. Instead of being titrated, the collected precipitate was ashed, the calcium being determined as CaO.

Urinary phosphorus content. Using 50 ccs. of urine, analysis was conducted exactly as in milk, with this exception that no copper foil was added.

7. Solid articles of diet, such as "diabetic rolls" were ashed and analysed in exactly the same way as were the faeces.

———ooo———

APPENDIX 2.

Case 1. M.R. aet.11 yrs – was admitted to hospital on 3.6.29 complaining of pain in the back, swelling of feet and ankles, general malaise and vomiting, all of 7 days' duration. On admission there was found slight oedema of legs and lumbar region: blood pressure 140/120 mms Hg: albuminuria 0.5 parts Esbach, with red and white blood cells and epithelial and granular casts.
Blood CO_2 52.9 vols.%: N.P.N. 45.4 mgs.%: Cl 325 mgs.%:
Serum Ca. 8.88 mgs.%: Serum inorg.P. 4 mgs.%.
The balance period was begun on 8.6.29 at which time the Esbach showed a trace of albumen and the urine still contained blood cells and casts. Blood curves were observed on 20.6.29 and 21.6.29.
The urine was noted albumin-free on 29.6.29 and the child was dismissed five weeks later in good condition. Diagnosis: "Acute nephritis".

Case 2. J.McG. aet.6 yrs. – was admitted to hospital on 24.5.29 because of headache, vomiting, swelling of face and red-coloured urine, all of one week's duration. On admission the face was puffy, abdomen full and tense. The urine showed albumin amounting to one part Esbach, red and white blood cells epithelial and granular casts. Blood pressure 135/90 mms Hg.
Blood CO_2 51.1 vols.%: N.P.N. 67 mgs.%: Cl 360 mgs.%.
Serum Ca. 7.76 mgs.%: inorg.P. 4.7 mgs.%.
The balance period began on 31.5.29 at which time the oedema was in process of disappearing and the Esbach reading was 0.25. On 7.6.29 oedema was entirely gone and blood pressure was 95/78 mms.Hg. 11.6.29 Serum Ca.9.28 mgs.%: inorg.P. 6 mgs.%
Dismissed well on 27.7.29. Diagnosis: "Acute nephritis".

Case 3. A.C. aet.12½yrs. – came to hospital on 12.12.28 because of vomiting and malaise for seven days; headache and swelling of face for 3 days; swelling of feet and oliguria of two days' duration.
On admission there was slight oedema of ankles and lumbar region and a blood pressure of 136/70 mms.Hg. Urine contained much albumin, blood cells and granular casts.
Blood CO_2 48.8 vols.%: N.P.N. 43 mgs.%: Cl 320 mgs.%
Serum Ca. 11.9 mgs.%: inorg.P. 4.13 mgs.%.
Blood curves were observed on 17 and 19.12.28. Blood pressure then was 116/58 mms.Hg.: Esbach 0.5 parts: and there were still some red cells and granular casts in the urine. The first balance period started on 30.12.28, the urine still containing a trace of albumin. On 3.2.29 the child developed diphtheria and was sent to I.D.Hospital where she was reported to be albumin-free. On 7.4.29 she was readmitted because of swelling of the ankles at night, but on admission no oedema was found. Blood pressure was 104/64 mms.Hg. and the urine contained albumin (1 part Esbach) and few red blood cells but no casts.
Five days later the urine was clear. Blood curves were repeated on 11 and 12.4.29 and the second balance period commenced on 15.4.29.
Patient was dismissed well on 14.5.29. Diagnosis: "Acute nephritis".

Case 4/

Case 4. N.J. aet.13½ yrs. - admitted 29.6.29 because of dyspnoea, headache and vomiting of three weeks' duration. Four years previously both kidneys had been decapsulated but the child had continued to have remittent oedema, headache and albuminuria. Shortly before admission she had severe epistaxis, and was drowsy but passed a fair amount of urine. On admission it was noted that she was pale with puffy face, oedema generalised; heart was much enlarged; blood pressure 172/150 mms.Hg; Esbach 11 parts, with abundant cells and casts in the urine.
Blood CO_2 44.5 vols.%: N.P.N. 153 mgs.%: Cl 340 mgs.%.
Serum Ca. 7.91 mgs.%: inorg.P. 12 mgs.%.
Blood curves were observed on the two days following admission and the balance period began on 4.7.29. Bowels were moving several times daily. On 8.7.29 the child became drowsy and dyspnoeic and complained of pain in the R.chest, which was explained by the finding of signs of a pericarditis on the following day.
12.7.29 Blood CO_2 46.5 vols.%: N.P.N. 353 mgs.%: Cl 470 mgs.%.
Serum Ca. 3.74 mgs.%: inorg.P.16 mgs.%.
Died 18.7.29. Diagnosis: "Chronic Parenchymatous nephritis".

Case 5. M.S. aet.9½ yrs. - admitted with bronchiectasis on 19.3.29: urine contained no albumin and no casts. On 3.4.29 there was very slight albuminuria and slight oedema of R.leg. A fortnight later there was nothing abnormal in the urine but the slight oedema persisted, and on 24.4.29 the child became drowsy and ill, and vomited twice. Later she had a generalised convulsion and had double optic neuritis, but no oedema. On 25.4.29 her condition remained unchanged except that there was much oedema and albuminuria with many granular casts. Esbach 14 parts.
Blood CO_2 54.3 vols.%: N.P.N. 97 mgs.%: Cl 290 mgs.%.
Serum Ca. 7.7 mgs.%: inorg.P. 4.44 mgs.%.
26.4.29 The child was still extremely drowsy and dazed and was quite blind. Oedema was less. Calcium curve was observed.
27.4.29 Consciousness was fully recovered: Esbach 1.75 parts, and urine contained no casts. Blood CO_2 49.4 vols.%: N.P.N.67mg%
Serum Ca. 7.87 mgs.%: inorg.P. 3.58 mgs.%, but again had convulsions.
On 30.4.29 a balance period was commenced, the oedema disappearing during the observation, with tremendous diuresis.
6.5.29 Blood CO_2 52.1 vols.%: N.P.N. 41 mgs.%: Cl 320 mgs.%.
Serum Ca. 8.91 mgs.%: inorg.P. 4.8 mgs.%. Calcium curve obtained.
Second balance period began on 2.6.29 when the urine contained a mere trace of albumin. Blood curves were followed on 21 and 25.5.29 and the child was dismissed well on 2.7.29.
Diagnosis: "Bronchiectasis, Uraemia".

Case 6 E.G.aet.6½ yrs. - was sent to hospital on 17.11.28 because of Polydipsia and polyuria, with a history of wetting her clothes and bed oftener than other children. At times her face had been puffy but no oedema had been noticed. She was found to be very small, without rickets, and to have albuminuria (0.75 parts Esbach) with many granular casts.
Blood pressure 104/74 mms.Hg.
Blood N.P.N. 120 mgs.%. Serum Ca. 10.19 mgs.%
Balance period was commenced on 3.12.28, the urine examination remaining unchanged. On 19.12.28 blood N.P.N. was 86 mgs.%.
Blood curves were followed on 16 and 17.1.29 and patient was dismissed in fairly good condition but with persistent albuminuria on 4.2.29.
Diagnosis: "Renal Dwarfism - chronic interstitial nephritis".

Case 7./

Case 7. A.R. aet.10½ yrs. - complained of three attacks of haematuria with pain on micturition and vomiting during the preceding three months.
On admission, 15.2.29 there was no oedema, blood pressure 136/94 urine contained albumin and blood with a few granular casts. Wassermann reaction was negative. Blood N.P.N.130mgs.%.
On 4.3.29 blood N.P.N. 40 mgs.% and blood pressure 94/60 mms Hg. Urine contained some red blood-corpuscles and an occasional granular cast. Blood curves were observed on 27 and 28.3.29 and the balance period started on 16.4.29.
On 1.5.29 there was still slight albuminuria with a few red blood cells. The blood Ca. curve was repeated on 2.5.29, and the child dismissed on 31.5.29 with a continuance of the slight haematuria.
He was seen as an out-patient on 2.7.29 and 7.8.29 on both of which dates albumen and red corpuscles were found in the urine, but no casts. His general health was excellent.
Diagnosis: "Acute nephritis".

Case 8. A.E. aet.6 yrs. - admitted 5.3.29, giving a history of sore throat with fever three weeks previously. For one week she had vomiting, swelling of face and feet, and for three days albuminuria and haematuria and abdominal pain.
On 7.3.29 face was puffy but there was no oedema. Blood pressure 102/80mms Hg. Urine contained albumin (1.5 parts Esbach) red blood corpuscles and epithelial casts.
Blood CO_2 58.9 vols.%: N.P.N. 57 mgs.%: Cl 350 mgs.%.
Serum Ca. 10.61 mgs.%: inorg.P. 4.89 mgs.%.
First balance period commenced on 8.3.29 and blood curves were observed on 22.3.29 and 8.4.29.
On 16.4.29 the urine was albumin-free and the second balance period began. Blood curves were repeated on 30.4.29 and 6.5.29.
On 13.5.29 blood pressure was 98/66 mms.Hg; urine remained albumin-free, and the child was dismissed well on 6.6.29.
Diagnosis: "Acute nephritis".

Case 9. F.E. aet.5 yrs. - had swelling of face and legs for two days prior to admission on 19.9.29 when he was found to have lumbar oedema, blood pressure 134/100 mms.Hg., albuminuria of 0.5 parts Esbach, with blood casts and granular casts in the urine.
Blood CO_2 62 vols.%: N.P.N. 37.5 mgs.%: Cl 320 mgs.%
Serum Ca. 9.95 mgs.%: inorg.P. 6 mgs.%.
Blood curves were observed on 21 and 22.9.29 while there was still marked puffiness of face and some oedema of legs.
25.9.29 blood pressure 100/65: oedema almost gone: very little albuminuria. On 27.9.29 the first balance period commenced, and on 9.10.29 the oedema had entirely gone and urine was clear.
The second balance period began on 14.10.29 and was followed by the second observation of blood curves on 22 and 23.10.29.
Diagnosis: "Acute nephritis".

Case 10. J.McD. aet.6½ yrs. - admitted on 20.2.29 because of swelling of face and scrotum with oliguria of four days' duration. He was found to have generalised oedema and wheezing all over both lungs. Urine contained albumin, red blood corpuscles and granular casts.
Blood CO_2 61.3 vols.%: N.P.N. 36 mgs.%: Cl 320 mgs.%.
Serum Ca. 8.07 mgs.%: inorg.P. 5.33 mgs.%.
The balance period commenced on 25.2.29 at which time oedema had almost diasppeared. Serum Ca. 10.17 mgs.%: inorg.P.4.44 mgs.%. 9.3.29 urine was reported free of casts, and albumin was present in very small amount. Blood pressure 90/60mms.Hg. Dismissed well 22.3.29. Diagnosis: "Acute nephritis".

Case 11/

Case 11. M.E. aet.8½ yrs. - admitted 14.11.28, complaining of pain in back and in abdomen for two weeks, swelling of face and high coloured urine.
Blood pressure was 120/85 mms.Hg., and urine contained albumin (0.25 parts Esbach) and some granular casts.
Blood CO_2 52.1 vols.%. Serum Ca. 9.3 mgs.%: inorg.P. 5.2 mgs.%.
On 21.11.28 the balance period began. Blood pressure was 102/52 mms.Hg., and the urine was clear.
Blood curves were observed on 13 and 19.12.28. There was a slight albuminuria in January 1929 which rapidly disappeared and the child was dismissed well on 2.3.29. Diagnosis: Acute nephritis".

Case 12. J.W. aet.12 yrs. - admitted on 22.5.29 with a history of haematuria, diarrhoea, vomiting, abdominal pain and generalised oedema with haemorrhagic areas on the skin, of 7 weeks' duration. He had suffered from several similar attacks previously, after the age of three years.
On admission, face was puffy, blood pressure 121/76 mms.Hg., albuminuria of 4.25 parts Esbach, with abundant blood cells and blood casts in the urine.
Blood CO_2 55.6 vols.%: N.P.N. 53.6 mgs.%: Cl 410 mgs.%.
Serum Ca. 6.6 mgs.%: inorg.P. 10 mgs.%.
For some time all attempts to obtain balance figures failed because of vomiting. On 7.6.29 the blood N.P.N. had risen to 193.5 mgs.%; serum Ca. was 4.35 mgs.%, and serum inorg.P. 12 mgs.%. (Table III).
Blood curves were first observed on 9 and 10.6.29 when a facial phenomenon was demonstrable (Chvostek's sign). There were no tubercle bacilli in the urine. Curves were repeated on 20 and 21.6.29.
On 11.7.29 Blood CO_2 51 vols.%: N.P.N. 59.1 mgs.%: Cl 330 mgs.%.
Serum Ca. 9 mgs.%: inorg.P. 5.58 mgs.%.
The third series of curves was obtained on 15 and 16.8.29 when the blood pressure was 120/85 mms.Hg; the Esbach had fallen to 0.75 - 1.75 parts, and the boy was generally much better.
The balance observations were commenced on 24.8.29, the Esbach still averaging 1+ parts daily.
Dismissed on 7.9.29 with persistent albuminuria but normal blood chemistry. Diagnosis: "Chronic parenchymatous nephritis."

Case 13. J.G. aet.10 yrs. - had suffered from thirst, polyuria and glycosuria for two years and was definitely known to have diabetes mellitus. Admitted 2.2.29 for regulation of diet.
First balance period, on free diet without insulin, commenced 8.2.29. Second balance period, on the same diet + 40 units of insulin daily, was observed from 13.2.29.

Case 14. J.McK. aet.7 $\frac{9}{12}$ yrs. - complained of frequency of micturition and polyuria, with great thirst of three weeks duration. She was found to suffer from diabetes mellitus, and was given a diet similar to "Case 13". (Table XXII).
First balance period began on 24.2.29, the second on 20.3.29.

Case 15. C.H. aet.7 $\frac{1}{12}$ yrs. - admitted on 26.6.29 with a history of vomiting and the passage of frequent green stools for three days, with delirium for two days. Diagnosis of acute ileo-colitis was made and patient made a good recovery. On 30.6.29 the urine contained blood and albumin but no casts, and on 11.7.29 after the temperature had subsided, urine was clear and continued so. Balance period commenced on 8.8.29 and blood curves were followed on 15 and 16.8.29.
Dismissed 17.8.29 - well.

Case 16/

Case 16. J.K. aet.6 yrs. - admitted 3.10.28 because of jerky movements of the limbs of four weeks' duration. Diagnosis: "Chorea".
Balance period commenced on 14.12.28 and blood curves were observed on 23 and 27.12.28. Urine was clear throughout his entire stay in hospital.

Case 17. E.McL. aet.6 yrs - admitted 29.6.29 with a history of severe cough and unpleasant sputum of three years' duration. She was considered as a possible bronchiectasis. Urine was always clear.
Balance study was commenced on 10.8.29 and blood curves were obtained on 16 and 17.8.29.

The other balance observations contained in Table VI were noted by Dr. Macrae in children convalescent from acute illnesses similar to those of Cases 15, 16, 17 of this series. Accordingly it has not been considered necessary to refer to their clinical histories.

———————oOo———————