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ELECTROLYTE DISTURBANCES IN SOME UROLOGICAL CONDITIONS

Summary of Ph.D. Thesis

Alison J. Dinwoodie B.Sc.

Department of Biochemistry and Department of Urology

Glasgow Royal Infirmary

1961

Changes in electrolyte balance have been studied in 3 groups of urological conditions, (1) in patients with ureterocolic transplants (2) in patients with acute renal failure and anaemia, and (3) in those with renal calculi. In addition a special study was made of changes in (4) magnesium levels and (5) blood cell potassium under the variety of conditions encountered.

1. In the patients with ureterocolic transplants hyperchloraemic acidosis was present in over 80%, in addition to a moderately raised urea. Hypokalaemia also occurred in a significant number. This imbalance was found to occur any time from a fortnight to a year or more following operation, with some stabilisation eventually taking place. Balance experiments showed that it was due to a disproportionate retention of chlorides. This was minimised by a low chloride diet and administration of sodium bicarbonate or lactate corrected the acidosis. Balance experiments also showed that considerable potassium deficiency could develop due to the increased excretion of potassium, and this was not always obvious from the plasma figures. In particular, rapid correction of severe acidosis led in many cases to marked hypokalaemia and unless precautions are taken this could be fatal.

2. In the patients with acute renal failure, changes in plasma electrolytes were followed from day to day. Comparison of plasma/

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phosphorus and urea levels were considered as an aid to prognosis, the relative height of the phosphorus occasionally giving an earlier indication of return of renal function. Some patients were treated with anabolic steroids, and although conditions were not always comparable, there was some benefit obtained.

3. Tests of parathyroid activity were investigated in patients with renal calculi. Factors affecting the tests, differential diagnosis and the value of repeated determinations are discussed. Calcium infusion tests and phosphorus/creatinine ratios were found to be of little value in borderline cases.

4. Serum magnesium was estimated in many of the patients referred to above. It tended to act reciprocally to calcium, for example, in the calcium infusion tests and the uraemic patients, but there was no definite relationship between it and serum potassium, e.g. in the potassium deficient patients and the uraemic ones, nor in the acidosis of the uraemic or transplanted patients. The effect of operation on serum and urine magnesium was also studied, but the effects were too slight for any significant trend to show. A few estimations were also made in patients with endocrine disorders, but results were again variable.

5. Blood cell potassium was estimated in many cases to evaluate its use as a guide to the state of body potassium. It was found that other factors affected it, in particular the state of acid-base equilibrium and the tonicity of the extracellular fluid, while in the potassium deficient patients it was often normal, and low in the anuric patients where there was no overabundance of potassium. A few tissue analyses were carried out which confirmed this. It was concluded that blood cell potassium estimations are unreliable guides to tissue potassium, unless these limitations are borne in mind.

ELECTROLYTE DISTURBANCES
IN SOME UROLOGICAL CONDITIONS.

Thesis presented for degree of Ph.D.

by

Alison J. Dinwoodie, B.Sc. (Glasgow).

Department of Biochemistry and Department of Urology,
Glasgow Royal Infirmary.

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SECTION I. GENERAL INTRODUCTION AND METHODS.

I A. Brief introduction to the five groups of studies.

The kidney plays such a vital role in maintaining body homeostasis that biochemical disturbances are an important feature of many urological conditions. In particular, the acid-base equilibrium and fluid balance are affected, thus altering the composition of the internal environment upon which depends the normal functioning of the various metabolic processes. The present studies were undertaken to observe these changes in particular cases, elucidate the underlying mechanisms, and whenever possible to minimise or prevent them. The choice of problems was governed largely by the clinical material available from the Urological Department, of which only a small proportion was suitable or available for full-scale investigations.

General disturbances in electrolyte metabolism have been investigated in three main groups of urological conditions, namely in patients with ureteric transplants, anuria, or renal calculi. In addition a special study was made of serum magnesium and blood cell potassium, under/

under the variety of conditions encountered. For the purpose of presentation, this work has been divided into these five separate sections, although there are naturally many cross-references, particularly between the last two groups and the first three ones.

I A1. Electrolyte imbalance in patients with ureteric transplants.

The greatest number of patients and those in whom the most extensive studies were made were those who had a transplantation of ureters into the colon, for varying reasons. In recent years it has been discovered that these people are particularly liable to develop an electrolyte disturbance, because apart from any renal impairment, there is the possibility of an additional load on the kidneys from substances reabsorbed from the urine across the intestinal wall. The development of this imbalance was therefore studied during the immediate post-operative period and at subsequent intervals. The long-term effect of the operation was also observed in patients operated on some years earlier, who reported at the Out-Patient Department at intervals for a general check. The control of this chronic impairment was undertaken/

undertaken, and particular attention was paid to those who had severe clinical symptoms as well, and who required immediate and more vigorous treatment.

I A2. Electrolyte changes in acute renal failure and anuria.

In patients with renal failure and anuria there are considerable changes in blood electrolyte composition when the normal homeostatic mechanism is impaired. This was the second group of patients to be studied. In a few cases an attempt was made to minimise these changes by reversing the cellular catabolism by administration of anabolic steroids. The importance of serum inorganic phosphorus estimations as an aid to prognosis has also been assessed.

I A3. Biochemical tests in the diagnosis of hyperparathyroidism in patients with renal calculus.

The discovery of parathyroid tumours in patients with renal calculi, with or without bone disease, has been increasing in recent years. This may be due in part to increased facilities for biochemical tests, but it is also due to recognition of the fact that the biochemical changes may be very slight, so that exploration of the glands/

glands is now being carried out in cases that previously would have been dismissed. In view of these slight alterations in blood chemistry which may be easily overlooked, a search has been made for other tests which would give a more sensitive indication of parathyroid activity.

I A4. Magnesium metabolism in various electrolyte disturbances.

As one of the principal cations of cells and extracellular fluid one would expect some variation in magnesium metabolism when the other electrolytes are altered. However in spite of the considerable amount of work on some electrolytes, magnesium has been largely neglected, and a definite relationship to the other ions has yet to be established. Many of the reports are equivocal or even conflicting; thus in renal disease the serum magnesium has been variously reported to be high, low, or normal. Serum magnesium was therefore estimated in many of the patients under different conditions during the course of the work, in the hope that some pattern would emerge.

I A5./

I A5. Factors affecting blood cell potassium.

There are comparatively few extensive reports on blood cell potassium levels in the various states where extracellular potassium is altered. The significance of potassium intoxication in acute renal failure or potassium deficiency in chronic renal disease, makes the study of the state of body potassium very important. The cells in blood would appear to be the most convenient source of intracellular potassium for investigation, but the connection between this and tissue potassium still needs definition. Again this estimation was carried out in several patients at various stages, in an attempt to clarify the situation.

SECTION I. GENERAL INTRODUCTION AND METHODS.

I B. Methods.

I B1. Collection of specimens.

10 - 20 ml. blood samples were collected in bottles containing heparin (4 mg./bottle) as an anticoagulant. Potassium oxalate (20 mg./bottle) was occasionally used as the anticoagulant, particularly for urea, phosphorus or phosphatase estimations. The plasma was generally separated within one hour of withdrawal, never later than two hours.

Urine was collected over 24 hour periods in winchesters containing 10 ml. conc. HCl when calcium and phosphorus estimations were required, but otherwise no preservative was used. The rectal fluid from the transplant patients was collected with the addition of 50 ml. glacial acetic acid to minimise the excessive alkaline decomposition.

Other data for metabolic balances were obtained by collecting all fluids, residues etc., and analysing suitable portions. Intake was calculated from $\frac{1}{4}$ samples of diet, which were homogenised, weighed, and aliquots analysed. These estimations were all done in duplicate or triplicate.

I B2./

I B2. Charting of data.

In graphing the metabolic data, the output has been plotted upwards from the base line, since we were primarily interested here in variations in urine output; also in some cases urine figures were available for a longer period than the actual balance, so that the chart could be continued without much alteration. Other losses e.g. gastric aspirate, have been added to this. The intake has then been plotted downwards from this level, and the balance indicated by cross-hatching. Thus cross-hatching present above the base line indicates that the losses have exceeded the intake and that a negative balance is present, while a positive balance is shown by cross-hatching below the base line. Contractions (not necessarily chemical symbols) for the various estimations are indicated in the methods section I B3.

I B3. Routine methods and accepted normal limits.

- (a) Alkali reserve. (Bicarbonate, HCO_3). The blood was collected under oil and alkali reserve estimated on plasma by the method of Van Slyke & Cullen (1917).
Normal range 23 - 30 meq./l. plasma.
- (b) Chloride (Cl). The blood was collected under oil
and/

and chloride was estimated in plasma and urine by the method of Van Slyke (1923). Normal range 96 - 107 meq./l. plasma. A simple modification of this method was used for food residues etc.: an appropriate amount (about 3g.) was weighed into a flask and digested for one hour on the steam bath with 10 ml. $\text{AgNO}_3/\text{HNO}_3$ reagent used in plasma Cl estimations. It was then made up to volume (100 ml.), filtered, and aliquots titrated with standard thiocyanate.

(c) Creatinine (Cr.) This was estimated in urine by the alkaline picrate reaction as given by King (1951).

(d) Inorganic phosphorus (P). This was estimated as inorganic phosphate in plasma and urine by the Fiske & Subbarow (1925) method as given by King (1951). Normal range 2.0 - 4.0 mg.P/100 ml. plasma. It has been reported (McGeown, Martin & Neill 1955) that heparin contains sufficient phosphorus to effect the result, but this was found to be negligible in the quantities employed here.

(e) Alkaline phosphatase (alk.p'ase) This was measured by the Bodansky method (1933) with estimation of phosphorus by strychnine molybdate precipitation (Tisdall 1922)/

- (Fisdall 1922). Normal range 1 - 4 Bodansky Units.
- (f) Proteins (Prot.) Plasma proteins were estimated by the biuret method of Gornall, Bardawill & David (1949), or by Kjeldahl digestion and Nesslerisation.
- (g) Urea (B.U.). This was estimated by the method of Archer & Robb (1925). Normal range 20 - 40 mg./100 ml. blood or plasma. In urine, it was estimated by the hypobromite method as described in Verley (1953).
- (h) Plasma and blood cell potassium. (K_p and K_c). Plasma was diluted 1 in 40 and read on the Eel flame photometer against a standard containing 0.125 meq. KCl/l. (equivalent to 5.0 meq/l. diluted 1 in 40). At these levels the intensity of emission is directly proportional to the concentration. Normal range 4.0 - 5.4 meq./l. plasma.

Blood cell potassium (K_c) was found by estimating whole blood potassium (K_b) and plasma potassium (K_p), and calculating from the haematocrit (H) the amount in the cells. Whole blood was diluted 1 in 500, in duplicate for reading. No correction was made in the haematocrit reading for plasma trapped by the cells, or for cell solids.

From/

From the formula $100 K_b = H \times K_c + (100 - H)K_p$

$$K_c = \frac{100(K_b - K_p)}{H} + K_p$$

A small series of 13 normals (obtained from blood donors at the transfusion service) gave a range of 90 - 102 meq./l., mean 97 meq./l., S.D. \pm 4.6 meq./l. This is in fair agreement with other reports e.g.,

Law, Stein & Meyer (1952) 99 cases, range 94-116 meq./l.

Hutt (1952) 14 cases, range 87-102 meq./l.

Knowles, Alverson &

Rubinstein (1955) 13 cases, range 86-102 meq./l.

- (i) Plasma sodium (Na). For the first year plasma sodium was estimated by precipitation with pyroantimonate and titration with iodide and thiosulphate (Kramer & Gittelman 1924). This method gives figures slightly higher than those normally quoted, the normal range being 141 - 152 meq./l. Later, satisfactory results were obtained with the flame photometer, using a 1 in 1000 dilution of plasma and comparison with a standard containing 0.140 meq. NaCl/l. Normal range is 135 - 147 meq./l., in agreement with other reports. 15 normal samples had a mean of 141 meq./l., S.D. 5.8 meq./l./

5.8 meq./l. It will be seen that some of the figures quoted for plasma sodium are apparently high, but if they are marked * and no comment made to the effect that they are abnormal, they will have been done before August 1955 by the pyroantimonate method.

(j) Sodium and potassium in urine, food, etc. All solutions were diluted to give concentrations of sodium and potassium similar to that of the standards used for plasma estimations. Gastric aspirates and rectal fluids were filtered first, the filtrates being diluted similarly.

Food residues (about 1 g.) were weighed and dry-ashed at 600°C. in the muffle oven, redissolved in 5 ml. N. HCl and made up to 100 ml., suitable dilutions being made from this for readings. Where total nitrogen was also being estimated, the solution after Kjeldahl digestion with conc. sulphuric acid and Selenium catalyst was sometimes used for potassium estimation, but variations were too great for this to be done for sodium as well.

I B4. Investigations into the estimation of calcium by flame photometry.

In/

In serum, calcium (Ca) was measured by the usual method of Clark & Collip (1925), this being the most generally satisfactory. Normal range 4.5 - 5.5 meq./l.

In urine, food and faeces, it was measured at first by the method of McCrudden (1911). This is a somewhat long and tedious method, so efforts were made to evolve a technique using the flame photometer. At the time although modified photometers had been used successfully no suitable method was available for the standard Eel photometer so that in the course of developing a method various factors had to be investigated.

(a) Effect of other ions. One of the main drawbacks is that the intensity of emission of calcium is greatly affected by the presence of other ions in the solution. Other cations generally increase its emission and in addition the main calcium emission line at 554 m μ is close to the sodium line at 589 m μ ; this interference was obviated by using a narrow interference filter from Barr & Stroud Limited with transmission at 620 m μ for one of the fainter calcium lines. Anions also exert a profound effect as is shown in Table I 1. It was thought that results obtained previously which gave variable answers and recoveries of only about 60% could be explained by the fact that solutions of/

TABLE I 1. Photometer readings of various calcium salts of the same concentration.

<u>Ca Salt</u> <u>(Ca conc. 1 meq./l.)</u>	<u>Galva reading</u>	<u>% of Ca CO₃ reading</u>
CaCO ₃ in 0.1 N-HCl	50	100
CaCO ₃ in 0.1 N-H ₂ SO ₄	33	66
CaSO ₄	35	71
CaC ₂ O ₄ in 0.1 N-HCl	32	64
CaC ₂ O ₄ in 0.1 N-H ₂ SO ₄	30	61
Ca ₃ (PO ₄) ₂	16	32

TABLE I 2. Variation of emission intensity of a solution containing 1 meq./l. CaCO₃ in different acid concentrations.

<u>Strength of acid</u>	<u>% of reading in 0.1 N-HCl</u>
0.05 N	102
0.1 N	100
0.2 N	96
0.5 N	90
1.0 N	85

of calcium oxalate in HCl were being read against a standard of CaCO_3 . Similar results were obtained by Margoshes & Vallee (1956) using different ammonium salts with calcium chloride solutions. They can be explained by the different volatility of the salts, some such as the chloride readily melting and dissociating (about 1600°C), while others such as the oxalate decompose first to give the oxide which is relatively refractory (M.P. 2527°C .). A very hot flame would minimise these differences but the gas/air mixture used routinely is relatively cool.

(b) Effect of acid concentration. Increasing the acid concentration in which the oxalate was dissolved was also found to affect the intensity of emission, as is shown in Table I 2.

(c) Effect of air pressure. Other factors such as air pressure also had to be controlled. For instance, by altering the pressure from 8 lb./sq. in. to 12 lb./sq. in. readings from 80% to 115% of that at 10 lb./sq. in. (normal reading pressure) were obtained.

(d) Method. It was apparent from these results that in order to compare any two calcium solutions by flame photometry/

photometry they must contain identical ions and be measured under constant conditions, the only variable being the concentration of calcium oxalate. When starting with a heterogeneous mixture such as urine, preliminary separation is necessary. Precipitation as the oxalate is the obvious method; this also brings down urates, which interfere with the permanganate titration (hence the preliminary abbing in McCrudden's method) but which do not appear to affect the flame photometry. The following method was therefore adopted:

The urine was adjusted to pH 4-5 and filtered. To 5 ml. were added 5 ml. Sulkowitch reagent, the solutions mixed and left for 2 hours. The precipitate was spun down and washed once with 2% ammonia, breaking up the precipitate, which was then spun down again. The precipitate was then redissolved in 1 ml. N. HCl, warming if necessary, washed into a 20 ml. graduated cylinder and made up to the mark with water, so that the final concentration of acid was 0.05 N. The solution was then read on the flame photometer, having previously set it with a standard solution containing 1 meq./l. calcium oxalate in 0.05 N.HCl. A standard curve was made up as it was found that direct proportionality did/

did not hold, especially at the higher range of readings. If the solution gave too high a reading it was diluted further with 0.05 N.HCl.

(e) Results. Using this method, reproducibility (21 tests) and recoveries (8 tests) were good, being within 2%, which compare favourably with other methods. In spite of the good recoveries however, there was a tendency for pure standards to come out high, up to 6%; results were also high for urine in comparison with the McCrudden ashing method, but results by direct precipitation and titration were even higher because of the co-precipitation of urates, which did not apparently affect the flame method. However, as it is very much quicker and more convenient to perform, this method was used for estimating urinary calcium, except in those instances where detailed balances were required and the absolute quantities more important.

I B5. Investigation of various methods of estimating magnesium.

Magnesium (Mg) was estimated by the method of Denis (1922) by precipitation and determination as phosphate. This is a rather long procedure involving two precipitations, as calcium has to be removed as a preliminary, so other methods/

methods were investigated. The method of Kunkel, Pearson & Schweigert (1947) has been advocated, which is a modification of Garner's (1946) using Titan Yellow. This method was tried but results were found to be very variable; the colour was somewhat unstable and the blank was very high, standard curves were not reproducible from day to day, and recoveries ranged from 91 - 107%. Other people have presumably experienced similar difficulties as numerous modifications have appeared e.g. Heagy (1948), Orange & Rhein (1951) Neill & Neely (1956).

Friedman & Rubin's method (1955) using the sequestering reagent E.D.T.A. and indicator Eriochrome Black T was also tried but the end-point was found to be very indistinct; calcium was estimated by difference between total divalent ions and magnesium, involving a larger error than normally tolerated. Smith (1955) has used Eriochrome Black T at an alkaline pH when it reacts with magnesium alone, but again results were not very reproducible and hindered by a very intense blank.

Results by the Denis method, using Fiske & Subbarow estimation of phosphorus, gave better results than any of the foregoing, standards, duplicates and recoveries being within/

within 3%, so this was the method used. The mean of 17 normal bloods was 2.1 meq/l., S.D. \pm 0.23 meq/l. which agrees with the usual accepted limits of 1.6 - 2.4 meq/l.

Other methods proposed also include precipitation of calcium oxalate followed by estimation of magnesium as the phosphate, but with alternative methods of phosphate determination e.g. Hoffman (1937), Simonsen, Westover & Wertman, (1947) or Davis (1955) but these did not seem to offer any advantage in time and manipulation.

SECTION II. ELECTROLYTE IMBALANCE IN PATIENTS WITH
URETERIC TRANSPLANTS.

II A. Introduction.

II A1. History.

In recent years it has been shown that patients in whom the ureters have been transplanted into the lower intestine are liable to develop a specific biochemical imbalance, manifesting itself mainly as a hyperchloraemic acidosis. Ferris & Odel in 1950 were the first to demonstrate in a large series of patients that the blood electrolytes were significantly abnormal. Prior to this it had been mentioned in a few isolated cases. Boyd (1931) tells of a child of 10 with a ureteric transplant 3 years previously who had a chronic acidosis with rickets. Jewett (1944) gives 33 case histories, but mentions the chemistry in only 3, two of whom had an acidosis, while two others died later of "uraemia." Flocks (1949) mentions it briefly in discussion, referring to Ferris' results, and there were two other papers in 1950 each describing a single patient (Diefenbach, Fisk & Gilson 1950, Foster, Drew & Wise 1950). Of interest too is one of the early reports on this type of operation; Turner (1929)/

(1929) in giving case histories of 17 patients happens to mention that in 5 instances potassium citrate had to be given for "acute pyelonephritis". One wonders if this were an instance of the right medication for the wrong reason.

Ferris & Odel carried out their survey on 141 patients operated on since 1939, and they found that as many as 79% had a raised plasma chloride and 80% a lowered plasma bicarbonate, while the blood urea was also raised in a considerable number. Definite clinical symptoms such as weakness, anorexia, nausea and a salty taste could be attributed to this and they were usually treated satisfactorily with alkalis and a low chloride diet. They suggested that the acidosis was due to an increased reabsorption of chloride from the urine in the bowel. As the plasma sodium was generally normal and there was no oedema, it did not seem to be absorbed with the chloride to any great extent. As evidence for the reabsorption of chloride from bowel rather than renal inability, they cited the facts that the hyperchloraemia only appeared after both ureters had been transplanted when the operation was done in two stages, and then only if sphincter control had/

had been regained; it was cured in one patient by rectal lavage and in another by nephrostomy.

Since their paper appeared there have been many references to the occurrence of electrolyte imbalance in ureteric transplant patients, for example, Doroshov (1951), Lapides (1951), Kekwick et al. (1951), Persons, Powell & Pyrah (1952), Wilkinson (1952) while Jacobs & Stirling (1952) carried out a survey for the British Association of Urological Surgeons, in which information was obtained on 201 patients. They found the bicarbonate was lowered in 78%, the chloride raised in 46% and the incidence of hyperchloraemic acidosis to be 40%. The % with raised Cl is lower than that quoted by Ferris & Odel, but can be explained partly by different limits set as normal (103 meq./l. by Ferris & Odel, 107 meq./l. by Jacobs & Stirling). Blood urea was raised in 72% and plasma potassium was lowered in 35%.

II A2. Evidence for reabsorption of chloride from the lower intestine.

The evidence for the reabsorption of chloride in the colon is fairly substantial. As early as 1919, Goldschmidt & Dayton showed that chloride could be absorbed or excreted/

excreted by the bowel, depending on the relative concentrations in the blood and lumen. They used dogs with isolated colons into which were introduced saline solutions of various concentration. At low saline concentrations, chloride was excreted and water was reabsorbed. If however, the blood chloride level were raised by saline infusions, this "threshold" was also raised. As these authors express their results in terms of NaCl, in the manner of the time, although actually estimating only the chloride, one cannot say from these results that the sodium behaved in an equivalent way. Visscher et al. (1944) used isotopic tracers in somewhat similar experiments in dogs. They found that reabsorption of water was very much faster from hypotonic solutions than from hypertonic ones, but the net movement from gut to blood in general depended on the direction and magnitude of the osmotic gradient. The rate of movement of chloride in to the blood increased with increasing concentration in the gut, but there was also a smaller reverse process independent of concentration. Absorption of chloride was also found in experiments in dogs by Boyce & Vest (1952) and Bohne & Rupe (1953),
the/

the latter also showing the effect of other ions on the speed of reabsorption. Thus phosphate increased the rate of chloride reabsorption, while it was also absorbed more quickly from isotonic saline than from isotonic ammonium chloride.

Parallel results were obtained in two patients by Annis & Alexander (1952). These had isolated colons, and when urine or saline was instilled, there was a markedly greater reabsorption of chloride than sodium. There was little change in volume, except when water alone was used. The acid urine became alkaline, and in the one patient in which it was observed the bicarbonate concentration increased. Urea concentration also decreased, but this may have been partly due to decomposition. In one case there was no change in potassium concentration, in the other there was a slight but significant increase. Parsons et al. (1952) also compared the composition of urine after being in the rectum, but indirectly. These patients had one ureter transplanted to the colon, the other remaining attached to the bladder, and as their kidneys had approximately equal function, the urine and rectal fluid were analysed for differences. The rectal fluid was/

was found to contain 60 - 80% less chloride than the urine, 30% less N.P.N., and slightly less sodium; potassium showed very little change, but was increased slightly in two out of the three. Similar results were obtained when the urine was introduced into the rectum, the alkalinity again increasing. In another paper Parsons (1952) used isotopes in a similar experiment to demonstrate the preferential reabsorption of chloride over sodium.

The above references are all concerned with ionic absorption from the rectum, colon, or caecum. When the ileum is utilised for a similar purpose, the results are slightly modified, and even conflicting. Thus Kekwick et al. (1951) report no change in urea or fluid balance and only a slight absorption of chloride when urine was introduced into an ileostomy in a patient with normal renal function. Pyrah et al. (1955) also demonstrated with isotopes that there was little net movement of sodium and chloride across the membrane in an ileal loop attached to the bladder; potassium was lost to the isotonic perfusing fluid, but was reabsorbed when the potassium concentration in the fluid was increased to that normally/

normally in urine. In contrast to this Eisenman & Bricker (1952) describe the reabsorption of chloride and 75% of the urea in a patient with a ureteroenterostomy into an isolated loop of ileum. However, none of his patients had an acidosis by six months following operation. Annis, Hunter & Wells (1953) record 4 patients with similar operations who had good biochemical and renal function within one year after operation but Wilson (1953) describes a patient who developed a hyperchloraemic acidosis 15 days post-operatively, so that even this operation is not free from biochemical hazards.

II A3. Part played by the kidney in the development of the imbalance.

From these experiments, it would appear to be established that chloride is reabsorbed from the bowel to a fairly marked degree, with sodium to a much lesser extent. The evidence for the reabsorption of urea is less conclusive, as decomposition also has to be taken into account. Potassium exchange is generally dismissed as negligible, but on closer examination of the figures given one finds that there is nearly always a slightly increased concentration in rectal fluid. The appearance of the hyperchloraemic/

hyperchloraemic acidosis with or without clinical symptoms would however appear to depend on other factors as well, in particular on the integrity of the kidney. Doroshow (1951) studied the electrolytes in 52 patients with ureteric transplants who had no renal impairment, as judged by excretion urography. Slightly under half this number had normal blood chemistry, while only 38% had a lowered plasma bicarbonate and 27% a raised chloride, figures which are considerably lower than the reported ones in the general surveys. Lapedes (1951) in his series of 22, reports that the 16 with biochemical imbalance had symptoms of pyelitis or poor renal function, while the remaining few were normal from both a biochemical and renal point of view. He also demonstrated the importance of good renal function in maintaining the balance in an experiment in which bladder urine was instilled into the rectum in 6 subjects, 3 normals and 3 chronic nephritics with poor renal function; the 3 with impaired function showed the characteristic abnormal electrolyte pattern, while the 3 normals were unaffected. Kekwick's (1951) 5 patients all with the hyperchloraemic acidosis also had impaired renal function. In the B.A.U.S. survey, over $\frac{3}{4}$ of those with hyperchloraemic acidosis had

a/

a raised blood urea and poor renal function; where the urea was normal, the kidneys were generally good, although the acidosis still developed.

II A4. Other theories.

While a large proportion of patients developing symptoms of hyperchloraemic acidosis definitely have a degree of renal impairment, there is too much evidence of electrolyte abnormality in patients with normal kidneys or minimal impairments for this to be the true causal factor. It has been suggested (Bohne & Rupe 1953, Wilson 1953, Care, Reed & Pyrah 1957) that the intestinal mucosa, and the kidney adjust themselves to the altered circumstances, the kidney excreting a larger volume than previously because of the increased load on it, in a manner analagous to the diuretic effect of ammonium chloride (Odel, Ferris & Priestley 1951), Parsons et al. (1952). A delicate balance is apparently achieved, but if there should be a slight stress or infection, this balance is upset, with rapid development of clinical symptoms. Whatever the cause of the hyperchloraemic acidosis, most people are agreed on the lines of treatment. Oral sodium, bicarbonate, citrate or lactate, with a low chloride diet are advocated for the general/

general treatment of every patient, with intravenous sodium lactate in the more severe clinical upsets.

The fact that this biochemical disturbance is a result of this operation has been confirmed beyond doubt, but understanding of the actual mechanism of development has progressed little beyond the theoretical stage, apart from establishing that chloride is definitely reabsorbed in the bowel. The part played by other ions has been largely neglected. Various theories have been suggested but with little evidence to support them, e.g., base loss from the bowel (Ferris & Odel 1950, Doroshov 1951, Parsons et al. 1952), kidneys failing to excrete acid, (Ferris & Odel 1950), chloride-bicarbonate shift (Parsons et al. 1952, Wilkinson 1952), NH_4^+ absorption (Parsons et al. 1952). By studying the development of the imbalance and the effect of treatment it is hoped that the studies presented here will be able to clarify some of the many points still awaiting an answer.

SECTION II. ELECTROLYTE IMBALANCE IN PATIENTS WITH
URETERIC TRANSPLANTS.

II B. Results.

II B1. Selection of patients.

Over the period September 1954 - August 1957, blood electrolyte determinations have been carried out in 93 patients with ureterocolic transplants. In many cases the tests have been repeated at intervals when the patients reported at the Urological Out-Patient Department.

They have been divided into two groups:

Group I consists of 40 patients who had their operation prior to September 1954; in 16 of these more than 7 years had elapsed since the operation was performed.

53 patients whose operation was performed during 1954-57 comprise Group II. For many of them it was a palliative procedure for bladder tumours, and several died within a year.

II B2. Incidence and types of electrolyte imbalance in
Group I patients.

The electrolyte results have been analysed from the 40 patients who have had three years or more in which to adjust to the altered conditions. A total of 204 estimations/

estimations have been made in these 40 cases, on three or more occasions in 24 patients, and in 10 only once.

16 of these 40 patients have had normal plasma electrolytes (sodium, potassium, chloride and bicarbonate) and urea, but of these only 3 patients have been consistently normal, so that no less than 92% have had one or more abnormal results at some time. The frequency of occurrence of the various types of abnormality is set out in Tables II 1 and II 2.

All possible combinations are naturally not shown, only those trends occurring regularly. For example, plasma sodium did not seem to be affected consistently, as it was raised or lowered in about an equal number, and in the large majority it was normal. Where it was above normal, it was generally associated with a very high Cl (more than 110 meq./l.) and where dehydration was also a factor.

As demonstrated elsewhere (Ferris & Odel 1950, Jacobs & Stirling 1952) a very large proportion of these patients had abnormally high chloride and urea results and a lowered bicarbonate. In addition potassium was significantly lowered in over half the number, a fact which has not usually been given so much prominence. The relatively frequent occurrence of hypokalaemia directed attention to
to/

TABLE II 1. Total numbers of abnormal plasma electrolytes.

	<u>Patients</u>		<u>Estimations</u>	
	No.	%	No.	%
Total	40		204	
Normal	16	40	24	12
Urea +	33	82	124	61
Cl +	34	85	126	62
HCO ₃ ⁻ -	33	82	138	68
K -	22	55	75	37
Na +	15	37	20	10
Na -	16	40	21	11

+ increased - decreased

TABLE II 2. Numbers of estimations showing various combinations of abnormal plasma electrolytes.

	<u>Urea+</u>	<u>Cl+</u>	<u>HCO₃⁻</u>	<u>K-</u>
Urea +	10			
Cl +	7	5		
HCO ₃ ⁻ -	12	22	6	
K -	10	2	5	3

	<u>HCO₃⁻-Urea+</u>	<u>Cl+Urea+</u>	<u>HCO₃⁻-Cl+</u>	<u>HCO₃⁻-Cl+Urea+</u>
K normal	12	7	22	43
K -	8	5	13	29

+ increased - decreased

to more particular investigations of potassium metabolism in this condition.

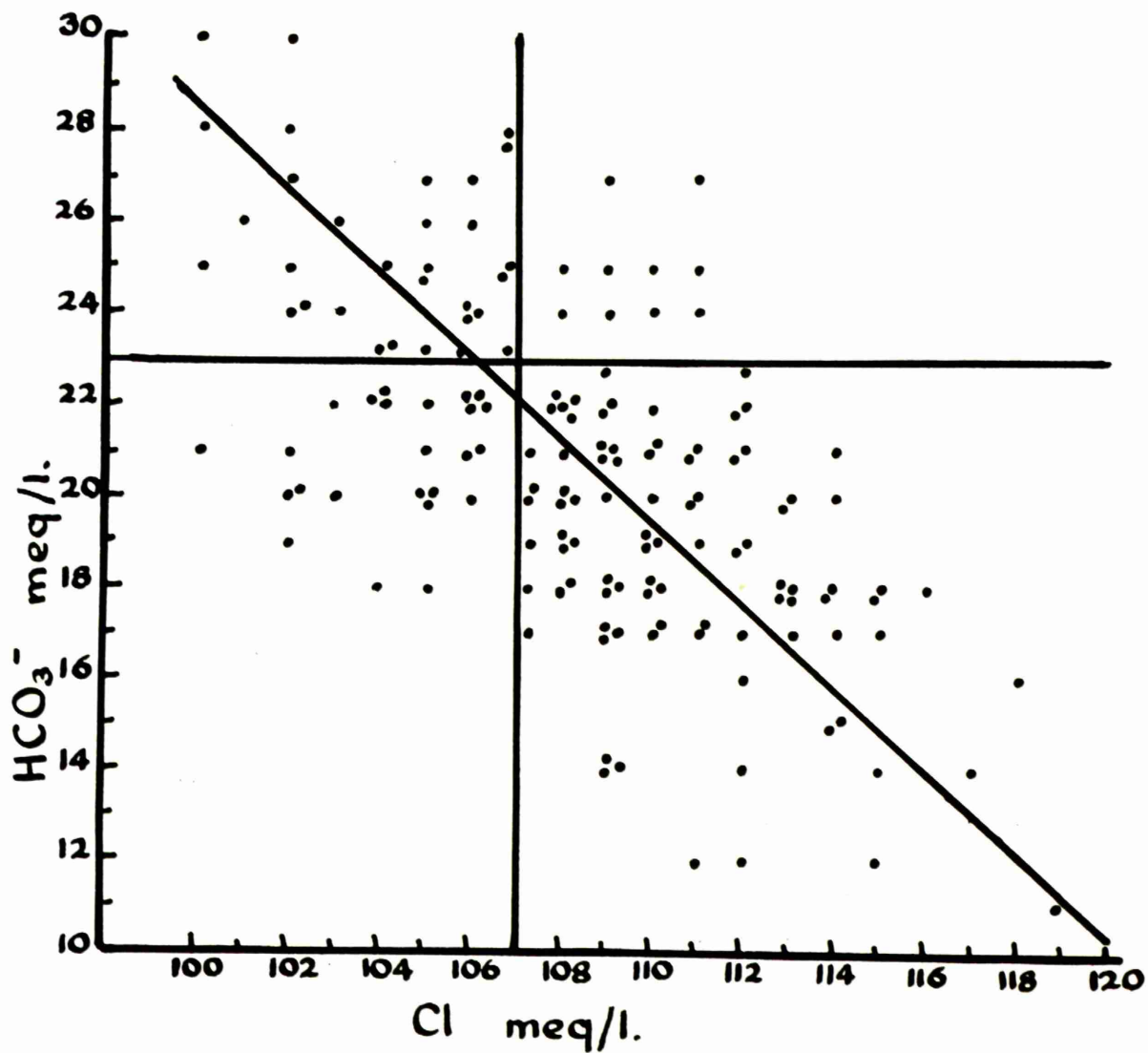
From Table II 2 some points may be made. Firstly, hyperchloraemia was rarely the sole abnormality, as might be expected if Cl retention were the only disturbance of metabolic function. The hyperchloraemia was most frequently found in association with a lowered bicarbonate (85%), the latter being depressed by an equivalent amount, as shown by the scatter diagram, Figure II 1. The subnormal bicarbonate was the most frequent abnormality found. This and the raised urea could be partly due to a degree of renal impairment. The hypokalaemia was most frequently associated with the acidosis or raised urea, rarely with the hyperchloraemia alone.

II B3. Development of electrolyte imbalance in the first few weeks following operation.

Obviously from the results given above a specific electrolyte imbalance is a frequent consequence of this operation. The development of the acidosis was investigated in several patients (Group II) from the immediate post-operative period onwards.

In 32 cases, plasma electrolytes were checked two or more/

Fig II, Scatter diagram of plasma Cl and HCO_3^-



more times in the first two weeks. Some examples are given in table II3. As might be expected, the normal changes consequent to any major operation were evident. In the first few days following operation plasma Na and Cl were generally below normal (60% - 19 out of 32 patients) although adequate saline was being given. There was usually an increase in plasma urea (78% - 25 patients) and some acidosis (47% - 15 patients), slight in most cases, but more severe in a few where rectal fluid output was poor (e.g. table II3, S.McK., C.B., J.G., V.G.) These all improved by the second week with ordinary treatment, with extra alkali when there was an acidosis. Plasma K was below 4 meq./l. in 69% (22 patients) frequently less than 3 meq./l. This hypokalaemia generally appeared in the second week, once the rectal drainage was well established and the output volume good (e.g. table II3, I.S., C.B., J.G.) It did not necessarily depend on a simultaneous acidosis or renal impairment as judged by a raised urea level. In some cases K returned to normal without any specific treatment, but in most instances potassium citrate was given orally (20-50 meq. daily, depending on the plasma levels.) One patient J.B., who had/

TABLE II 3. Examples of plasma electrolyte results in the first fortnight following operation.

<u>Patient</u>	<u>Day after operation</u>	<u>K</u>	<u>Na</u>	<u>Cl</u>	<u>HCO₃⁻</u>	<u>B.U.</u>	<u>Remarks</u>
			<u>meq./l.</u>			<u>mg./100 ml.</u>	
I.S. F.54 yrs.	-1	4.0	*150	102	26	23	Na, Cl fell
	1	4.2	*147	99	25	39	Urea rose.
	4	3.9	*140	93	26	80	
	13	2.8	*141	89	30	43	K low 2nd week
C.B. F.55 yrs.	-1	5.0	130	98	29	27	Na, Cl fell
	1	4.4	131	96	25	66	Urea rose.
	3	5.1	122	87	23	105	
	9	3.1	123	90	22	75	
	13	3.0	128	97	23	55	K low 2nd week
J.A. M.61 yrs.	-1	4.8	130	100	26	29	Na, Cl fell
	1	4.9	132	92	26	54	slightly.
	3	4.7	128	89	27	41	
	5	4.1	133	92	26	31	Slight rise
	10	-	135	95	31	35	in urea.
J.G. M.62 yrs.	-5	3.5	141	99	24	46	Na, HCO ₃ ⁻ fell
	2	4.4	129	98	18	82	Marked rise
	4	4.5	130	97	14	168	in urea.
	5	4.1	134	99	15	183	
	7	3.2	133	105	20	85	Marked fall in
	9	2.9	132	102	23	48	K, 2nd week.
	11	2.5	130	97	22	34	+Received 36meq K, 8th-11thdays

+ K given as citrate and Na as bicarbonate unless otherwise stated.

* Na figures approximately 10 meq. too high by old method. (See Methods ID 31)

TABLE II 3. (Contd.)

Patient	Day after operation	K	Na	Cl meq./l.	HCO ₃ ⁻	B.U. mg./100 ml.	Remarks
J.L. M.63 yrs.	-10	4.5	138	101	27	48	Cl retention and equivalent: sent acidosis by 2nd week. Urea increasing.
	1	4.9	141	99	25	44	
	7	3.5	137	99	28	38	
	13	5.0	140	111	17	57	
V.G. F.64 yrs.	-1	4.1	142	102	26	22	Na, HCO ₃ fell. Urea increased.
	1	3.8	129	102	22	34	
	3	4.6	127	96	18	110	
	5	3.5	131	98	16	110	
	8	4.1	135	99	27	61	
	15	4.4	133	107	25	36	
M.H. F.63 yrs.	-1	4.1	136	101	27	26	K low.
	1	3.8	130	96	23	42	
	4	3.4	133	92	27	39	
	6	3.7	130	90	27	38	
	14	3.3	150	108	28	63	
S.McK. F.36 yrs.	-2	3.7	140	103	26	34	Na, Cl, HCO ₃ fell, urea rose.
	1	4.1	136	98	26	38	
	5	3.6	130	93	19	85	
	7	3.7	128	102	20	48	
	14	4.0	134	101	26	24	

+ K given as citrate and Na as bicarbonate unless otherwise stated.

* Na figures approximately 10 meq. too high by old method. (see Methods IB 3i)

had a low plasma K pre-operatively, received 50 meq. K daily except for the immediate days following operation; he was one of the few who did not develop a hypokalemia.

By the end of the first fortnight, 3 of the 32 patients had already developed hyperchloraemia simultaneously with acidosis (e.g. Table II 3, J.L.); another patient had had a high Cl before operation, and it never fell below 107 meq./l. during the whole period. Another 5 patients had a Cl at the upper limit of normal, (e.g. Table II 3, V.G., M.H.) so that even at this early stage some evidence of imbalance was already apparent.

In 16 of these patients, plasma electrolytes were checked at intervals to the end of the month. 5 of the 16 showed no indication of Cl retention or acidosis, and another 3 had a plasma Cl at the upper limit of normal. Of the remaining 6, all of whom had had signs of Cl retention after the first fortnight, 3 were now improved to normal (only one of whom had been taking extra alkalis) and 2 were unchanged, so that some stabilisation was taking place. In 9 of the 16 patients, plasma K was below normal; only 2 of these were receiving K supplements, and their K was gradually improving. 4 others also receiving extra K/

K now had normal plasma levels.

14 patients, other than these mentioned above, in whom electrolyte estimations were done post-operatively, died within a month of operation. All these patients had bladder tumours. One patient developed a marked hyperchloraemia but without acidosis at 7-10 days (Cl 114, HCO_3 23 meq./l., B.U. 237 mg./100 ml.), and one other was slightly affected. (Cl 108, HCO_3 22 meq./l.) In the other patients, electrolyte results were those of renal failure, i.e., high K and B.U., low Na, Cl and HCO_3 , and cause of death could not be attributed directly to the electrolyte imbalance specific to this operation.

II B4. Balance experiments in the immediate post-operative period.

To extend the interpretation of these results, balance studies were undertaken in two patients, R.A. and W. McC. In the case of R.A. the Na Cl intake was not actually analysed but was calculated from tables by the diet kitchen. This is not a very satisfactory procedure, so in W. McC. the intake was analysed daily, with the addition of any intravenous supplements. In a third patient B.McA., who died 9 days after operation, the output/

output was measured, and as I.V. fluids constituted virtually his total intake, the balance could be calculated. The data for R.A., W.McC and B.McA are charted in Figures II 2, 3 and 4 respectively. For the method of charting balance data see Methods, Section I B2.

Blood results: The plasma levels in R.A. and W.McC were not grossly abnormal postoperatively. Within 3 days of operation both showed a decrease in Na, Cl and HCO_3^- , and an increase in K and urea, all of which were more pronounced in the case of W.McC. These figures show the same pattern as those mentioned in the previous paragraph. In B.McA. the results were similar only more exaggerated, but instead of improving after the 4th - 6th days they continued to deteriorate, particularly the urea and K indicating a degree of renal failure.

Urine* results: The concentrations of Na and Cl in the urine (rectal fluid) were very low for the first 2 or 3 days post-operatively (less than 15 meq./l.) and in addition the fluid volume was small, so that losses were slight; as intake was adequate, salt retention took place, this/

* "Urine" in these patients refers to the rectal fluid.

Fig 1a. Balance data in the operation period in transplant patient R.A.

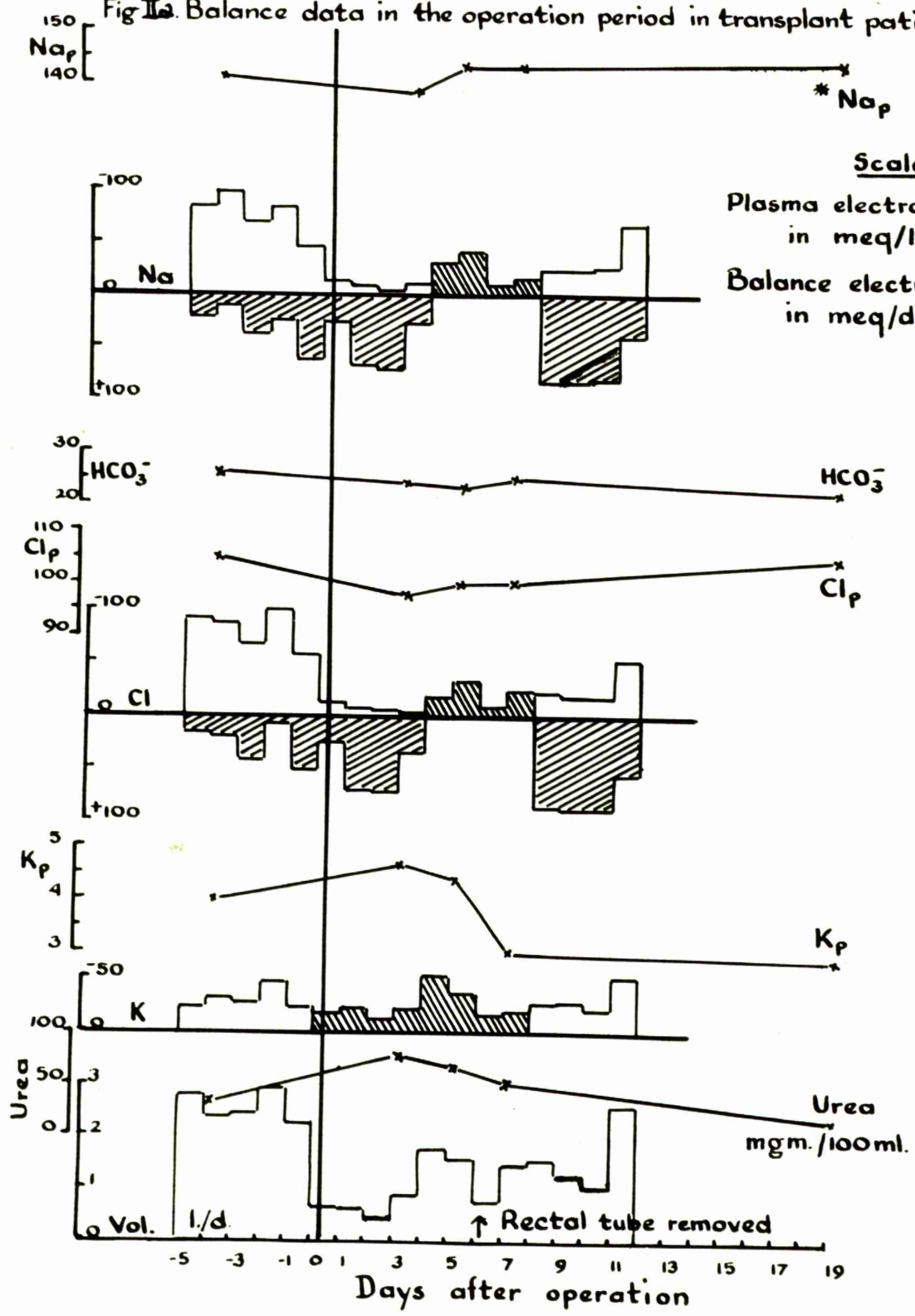


Fig 13. Balance data in the operation period in transplant patient W.M.C.

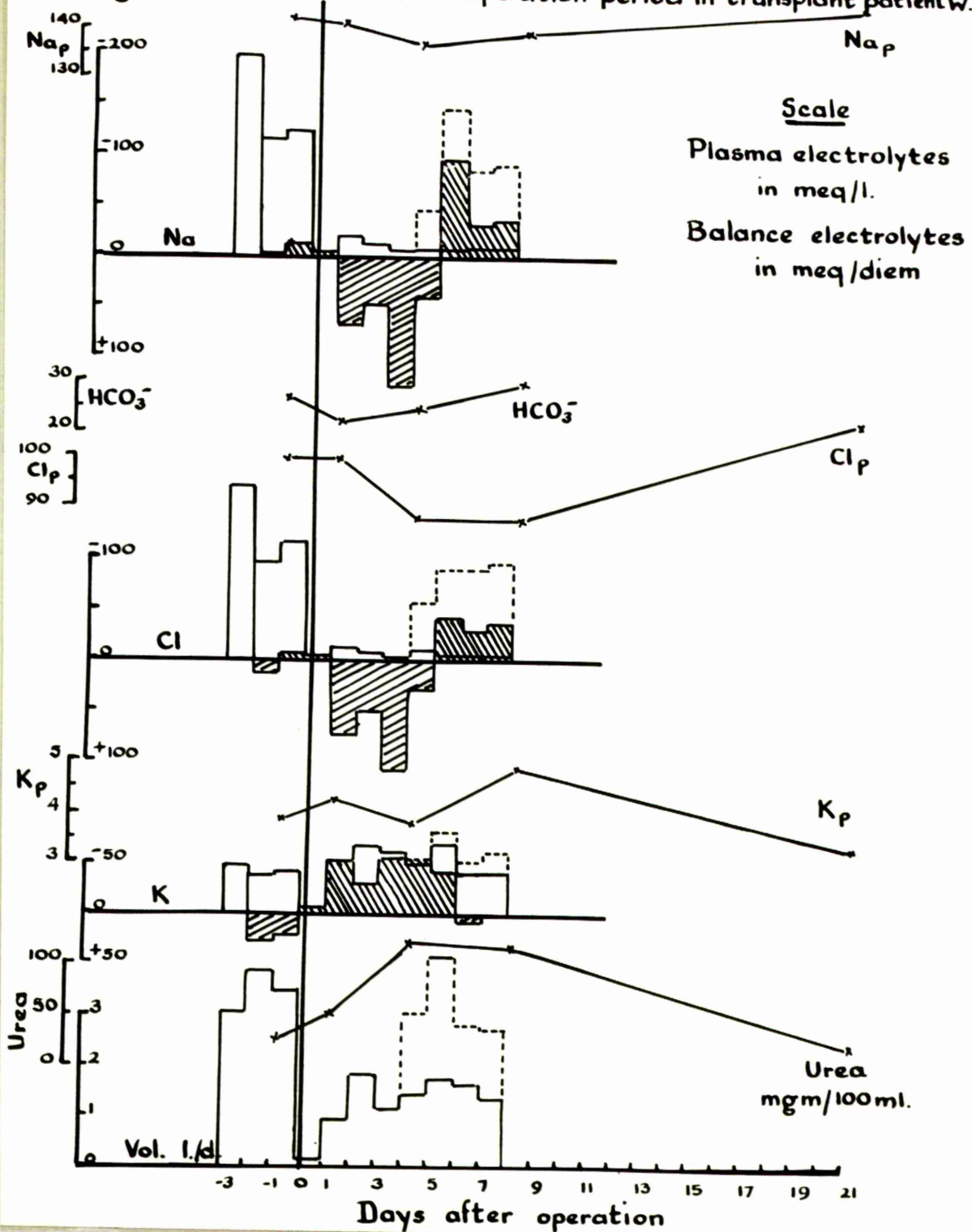
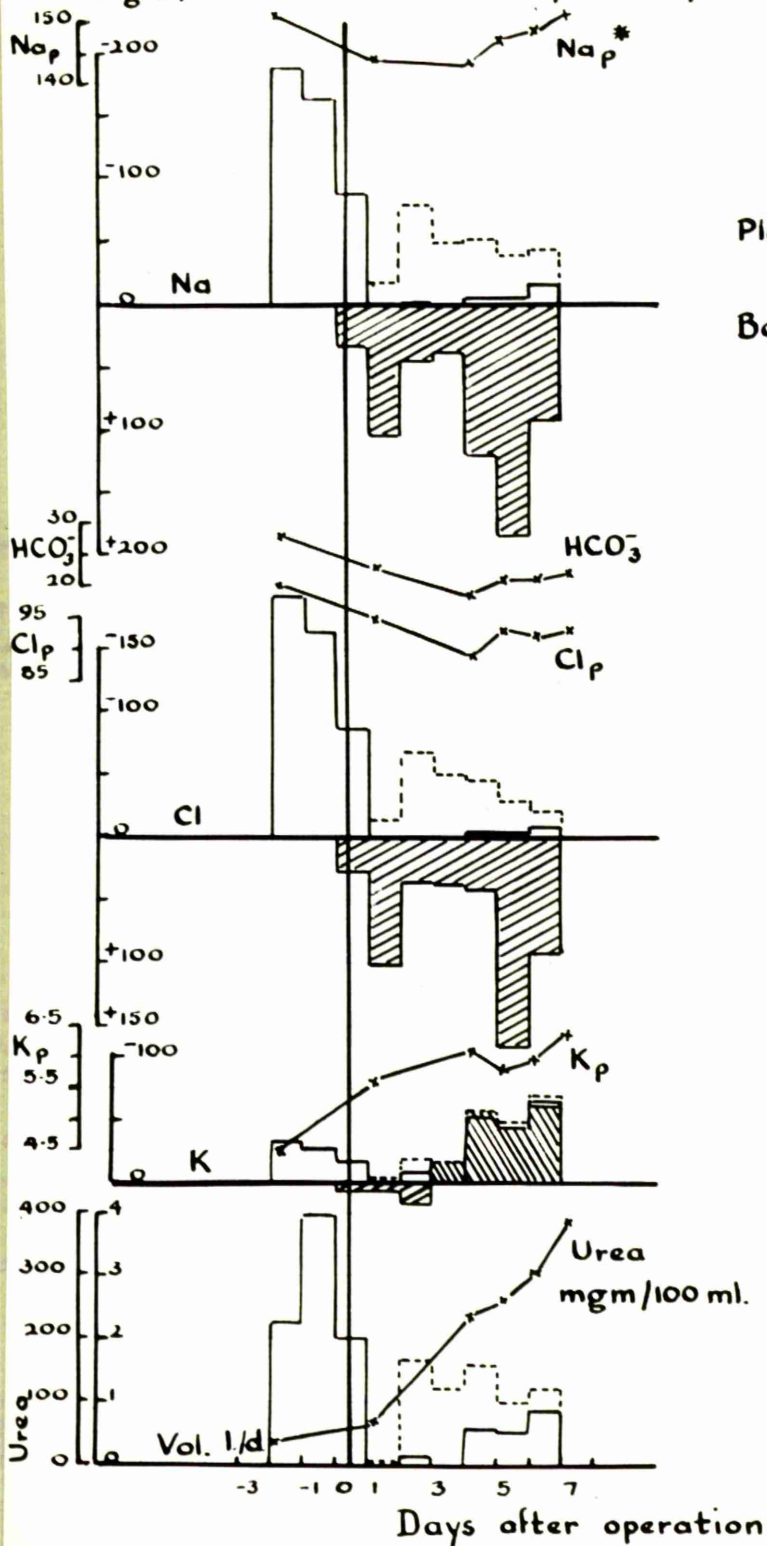


Fig 14. Balance data in the operation period in transplant patient B.McA.



this being the usual response to surgical stress. As the plasma levels decreased, there must have been considerable expansion of the extracellular fluid with water retention. This emphasises again that a low plasma Na or Cl in the first 3-4 days following operation does not necessarily indicate a salt deficiency, especially if the urine volume is low, and administration of saline will only flood the tissues while having little effect on the plasma levels. Losses from gastric aspiration may be considerable and must be replaced, as was necessary in the cases of W.McC. and B.McA.

As regards K excretion in the rectal fluid, its concentration was greater than pre-operatively (averaging in the 3 cases 36 meq./l. as against 12 meq./l. previously). For the first few days there was generally a small volume of rectal drainage, so losses were slight, and this coupled with the release of cell K as a result of post-operative catabolism would more than account for the slight rise in plasma K. As the fluid volume excreted increased, so the K losses continued, although catabolism was decreasing and as intake was still poor, the negative balance was reflected by the lowered plasma K. For example, R.A. lost 115 meq. in the 3rd - 6th days, and W. McC. lost 213 meq. in the same/

same period. The latter's plasma K, after showing a transient fall, actually had risen by the end of this time, and as his urea had also risen cell catabolism was evidently continuing. Catabolism also continued in B.McA., whose plasma K and urea increased gradually over the whole period; the fluid volume excreted was very small, but as the K concentration was high losses came to 140 meq.

In R.A., the Na, Cl balance was carried on after removal of the rectal tube on the sixth day. The Na, Cl, K and volume output had all been increasing prior to this, but all were diminished when the continuous drainage stopped, gradually increasing again later. It was noticeable that Na excretion was generally slightly greater than the Cl although the intake of both was identical, so that in the four days 32 meq. Cl more than Na had been retained.

Three weeks after operation, plasma Cl had increased in both H.A. and W. McC., although in the former it was only back to the pre-operative level. Bicarbonate was at the lower limit of normal, and plasma K was also low in both/

both cases.

Conclusions: The balance data taken in conjunction with the several blood results mentioned in Section II B3 indicate that in the immediate post-operative period, changes in plasma electrolyte composition are those of a normal reaction to stress. In particular, a low plasma Na and Cl are not indicative of salt deficiency, unless definite losses can be demonstrated e.g., in gastric aspirate. On the other hand, the subnormal K which generally appears in the second week may be partly due to the altered pathway of urine excretion since the K concentration in the rectal fluid was on the average somewhat higher than in the previous urine, and if the fluid output is high a considerable deficiency may quickly develop unless a reasonable K intake is assured. By the second week it was also apparent in the one figure available (R.A.) that there was an unequal excretion of Na over Cl, and in a small number of patients hyperchloraemia was first apparent at the end of the first fortnight, although acidosis was less obvious.

II B5. Electrolyte changes in the first year following operation.

Plasma/

Plasma electrolytes were estimated in 25 patients at varying intervals in the first year following operation, 21 of whom were included in the previous chapter. The death occurred of 10 of this number within the year. In only 2 instances was there a marked hyperchloraemic acidosis when last seen, although 4 had hypokalaemia. 3 of them died in hospital, with electrolyte results typical of renal failure in 2 instances, one of them (P.W.) having a marked hyperchloraemia as well which responded only temporarily to treatment. Of the 7 who died at home, the urea was only slightly raised in 3 (less than 60 mg./100 ml.) when they last reported as out-patients so renal failure was not obvious then.

On the 15 remaining patients, after one year 5 had a marked hyperchloraemic acidosis and urea over 70 mg./100 ml. It was noted that 7 others had had at one time the typical acidosis, but by the end of the year had reverted to normal, although urea was still slightly raised (50-80 mg./100 ml.) This could indicate a certain amount of readjustment by the body, although they were also receiving extra alkali.

Potassium was low in 4 patients at the end of the year, and in 3 others had returned to normal from a previous low/

low level. The hypokalaemia showed no particular correlation with the development of the acidosis, but seemed to occur independantly. Thus there was no statistical difference between the Cl and bicarbonate levels in those with either a normal or a low K. Of interest in this connection was J.C., who developed a fistula shortly after operation, so that there was continuous drainage for 3 months until the ureter was re-implanted; during this period there was no indication at all of Cl or urea retention, but his plasma K remained low until sufficient was given orally, (36 meq. KCl/day). One month after re-implantation, a raised urea and slight acidosis were present, but the K was now normal.

The raised Cl generally appeared simultaneously with the reduction in bicarbonate, the two being practically equivalent, with Na maintained at normal levels nearly all the time. 4 had an acidosis and raised urea before development of hyperchloraemia, while in 2 others the hyperchloraemia came first. These figures agree substantially with those found in the Group I patients (Section II B2). None of the patients showed completely normal results for the entire year following operation.

II B6/

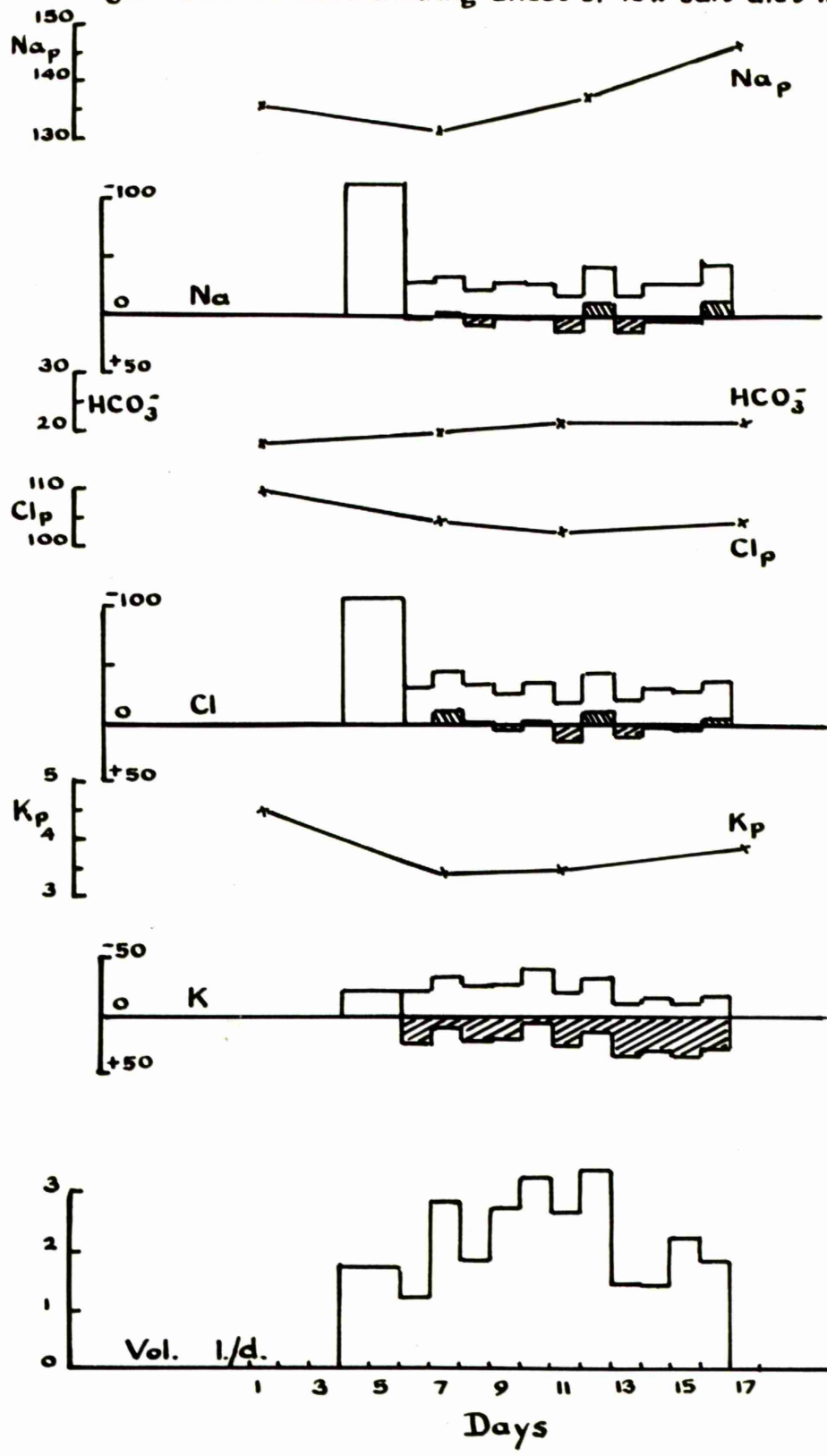
II B6. Balance data on 4 patients on various diets.

With the exchange of substances between the urine and the extracellular fluid across the intestinal mucosa the composition of this fluid will not be so readily adjusted to changes in intake or other circumstances as in the highly specialised renal tubules. By varying the dietary intake and estimating the losses, it was hoped to find how rapidly and to what extent adjustments could be made. This was done in 3 patients, A.H., J.Q., and J.C., who had the ureters transplanted several years previously, and in R.M., who was still convalescing from the operation, but who had already developed a hyperchloraemia acidosis. All had some degree of Cl retention and acidosis before commencing, and the intention was to see whether retention still occurred when dietary Na and Cl were restricted; also if K could be conserved adequately on a low intake. Actually the K intake was higher than had been intended, but this was not discovered until the food was subsequently analysed.

J.Q. (Figure II 5) adjusted output to balance intake immediately after starting the low NaCl diet and remained in balance the whole time with only minor fluctuations.

In/

Fig 15. Balance data showing effect of low salt diet in transplant patient J.Q.



Scale
 Plasma electrolytes
 in meq/l.
 Balance electrolytes
 in meq/diem.

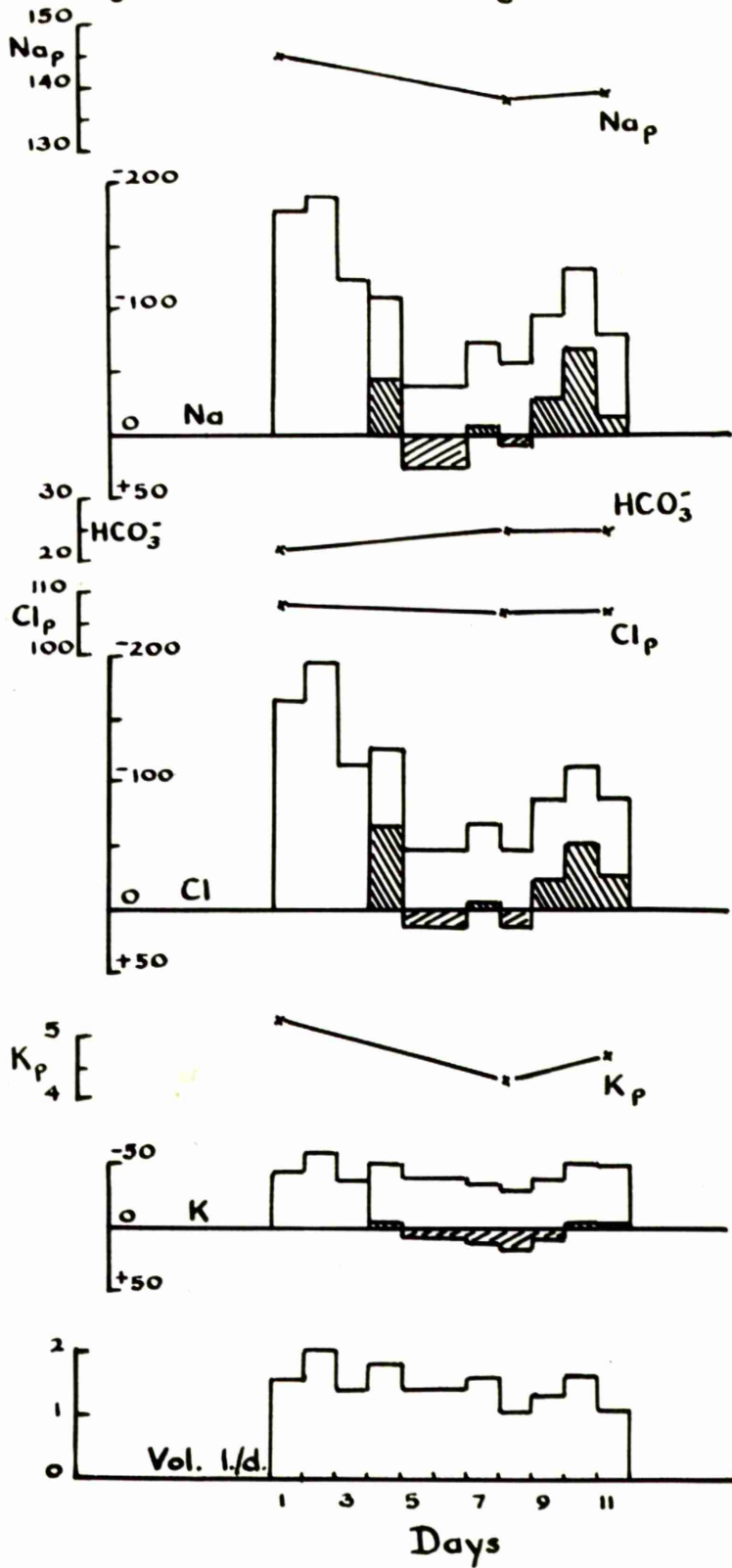
In spite of no extra Cl loss, the plasma level improved from 110 to 103 meq./l., with a similar rise in the bicarbonate to compensate. The plasma Na meanwhile rose, although there was no significant retention, this could either be because of haemoconcentration or by a movement from the cells into the E.C.F. Although there was an increased urinary volume and the plasma K and HCO_3^- also rose by a corresponding amount, the Cl did not, which if there was a contraction in extracellular volume would imply a very large shift of Cl to some other part of the body, apparently unbalanced by other ions. The more likely explanation is a movement of Na out of the cells, its place being taken by K. The amount of K retained - and there was a positive balance for the whole period - was 238 meq. in 11 days, the increase in the Na in the E.C.F. being equivalent to roughly $\frac{2}{3}$ of this (a rise of 12 meq./l. in approximately 12 l. E.C.F. = 144 meq.) while the increase in E.C.F. K would account for only 5 meq. at the most. It is worth mentioning here the presence of a normal plasma K level in conjunction with a presumed tissue deficiency, followed by a low K level with K retention and correction of the acidosis. This point will/

will be mentioned later. The patient had originally been admitted for some inflammatory condition, but had recovered by the time this balance was started, so it is conceivable that this had caused a subclinical K deficiency, which was not evident from the plasma levels because of the chronic acidosis.

Adjustment to the low Na and Cl diet in A.H. (Figure II 6) was more erratic, and the first day on the diet there was practically no decrease in the amount excreted. This was followed by a few days positive balance with a lower excretion but by the end of the week this had risen again so that there was an overall negative balance of 109 meq. The plasma levels remained little changed although there was a slight fall in the Na. K also decreased in the plasma, although there was a slight retention over most of the periods (43 meq. in eight days.)

The patient R.M. (Figure II 7) was really in a different category in that the operation had only been done recently, so that he had scarcely had time for adjustment. Also his Cl was high even before operation, so that the renal tubular function was suspect. There are several points of difference between this patient and the preceding ones/

Fig II 6. Balance data showing effect of low salt diet in transplant patient AH.

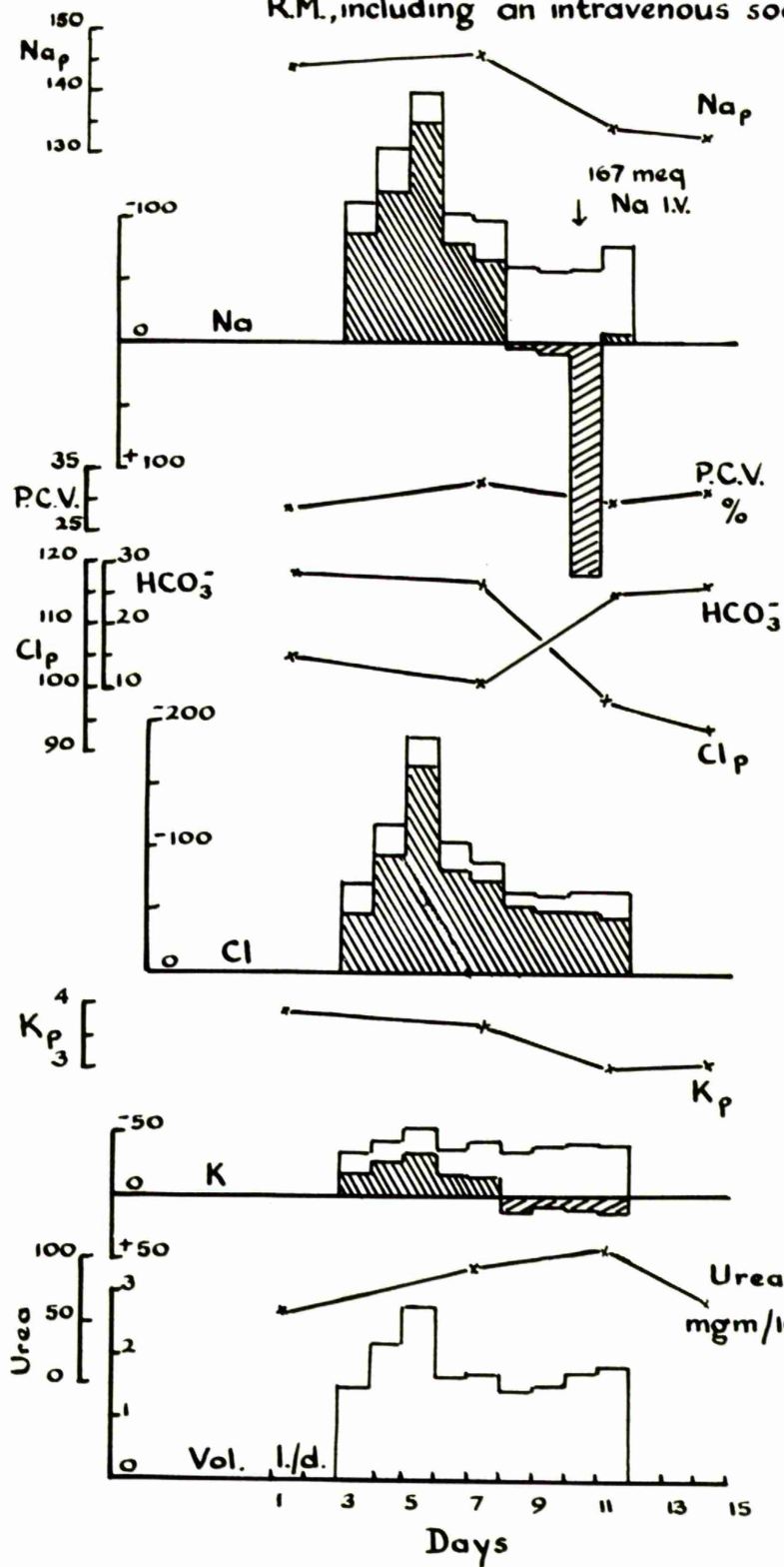


Scale

Plasma electrolytes
in meq/l.

Balance electrolytes
in meq/diem

Fig II 7. Balance data showing effect of low salt diet in transplant patient R.M., including an intravenous sodium lactate infusion.



Scale

Plasma electrolytes
in meq/l.

Balance electrolytes
in meq/diem.

ones. Firstly, he showed little conservation of Na, Cl or K when these were restricted in diet. In spite of a large urinary output of Na and Cl, the plasma levels did not change much, and the acidosis increased. Sodium bicarbonate and potassium citrate were given orally for two days, but as the patient was still nauseated and ill, 1 litre $\frac{1}{6}$ molar sodium lactate was given intravenously. This resulted in an immediate improvement in the acidosis with an increase in HCO_3^- of 14 meq./l., a corresponding decrease in Cl of 19 meq./l., but also a decrease of 12 meq./l., in the Na. These changes were not accompanied by any outpouring of Na and Cl in the urine, the amount excreted remaining remarkably steady. Again the explanation could lie partly in the expansion of the E.C.F., in this instance supported by the haematocrit values which fell by 3%. A rough calculation shows that in spite of the apparent fall in plasma Na, expansion of the E.C.F. by 0.5 l. (expansion of 14 l. E.C.F. by 3%) accounts for more than half of this; likewise the drop in Cl is not really so spectacular as it seems, being partly due to dilution. The previous strongly negative Na and Cl balance can also be partly explained by a contraction of E.C.F. volume;

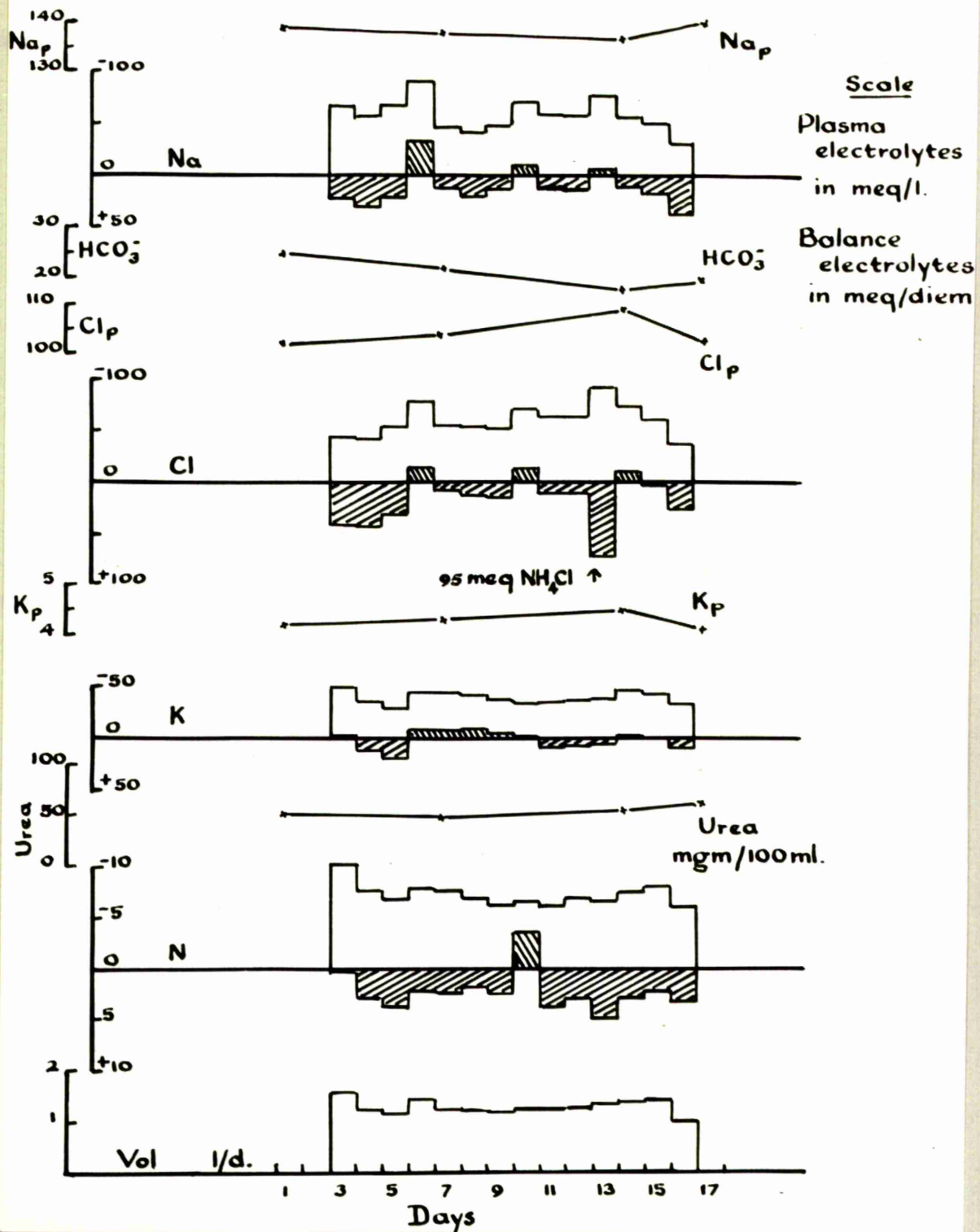
the/

the haematocrit rose from 29% to 33% in the first 4 days, corresponding to nearly a litre of E.C.F. lost.

The urinary K meanwhile remained very constant over the whole period. The diet contained only about 25 meq. and when this was the sole source it proved inadequate, and a negative balance was present with a falling plasma K. By giving potassium citrate (36 meq./day), the balance became positive, although the amount excreted did not vary. When the I.V. lactate was given there was again a marked fall in plasma K coincident with a positive balance, again demonstrating the shift of K into the tissues with increasing alkalinity, and without altering the amount excreted.

The fourth patient J.C. (Figure II 8) had her ureters transplanted over 20 years ago, and had been re-admitted on this occasion for a plastics operation. A few months previously she had been admitted to hospital with a severe hypokalaemia and acidosis, and a balance was done at the time, (see later Section II B8). As she was now in very much better health and had recovered very satisfactorily from the operation, the opportunity was taken of repeating the balance. There was a slight retention of Na and Cl, but otherwise nothing of note. It was decided to try the/

Fig 11a. Balance data in transplant patient J.C., including an acid-loading test.



the effect of an acid-loading test, by giving 5 g. NH_4Cl orally. The first time (10th day) it made her vomit, but using cachets, she tolerated it better the second time (13th day). This produced only a very slight rise in the amount of Cl excreted, the bulk of it being retained and resulting in a raised plasma Cl with the bicarbonate correspondingly depressed. The increased Cl excretion was matched by an increase in urinary Na, but the K was hardly affected at all, the plasma level only rising very slightly. However, two days later the plasma Cl had returned to normal, although the excess had not apparently been removed. There was a positive nitrogen balance over the whole period, which was probably a result of convalescence following the operation. The NH_4Cl made little or no difference to the nitrogen balance, accounting for only about 0.1 g. N.

Conclusions: From these four balances one or two points may be made, particularly with regard to potassium. The K excretion varied very little with change in diet; there was no difference between the days before the diet and during it in J.Q. and A.H., although figures for the intake in the first days were not available. There was no difference/

difference in K excretion in R.M. when his intake was doubled, and he was also unable to conserve it on the low intake, so that if this had been allowed to continue a deficiency would soon have developed. On correction of the acidosis in the first three patients, there was a movement of K into the tissues, shown by a falling plasma level coincident with a positive balance. In J.C., after producing an acidosis, there was a slight increase in plasma K suggesting a move in the opposite direction. Neither the I.V. lactate nor the ammonium chloride appeared to alter the urine K excretion; in fact the concentration of K in the uring was remarkably constant under the different conditions. In other words, the control of K excretion may be impaired as a result of transplantation of the ureters into the colon.

Although K excretion was relatively unaffected by varying the diet and thus not conserved efficiently, Na and Cl excretion was rapidly adjusted to the intake and balance soon attained. A transient lowering of plasma

Cl occurred in J.Q. on decreasing the amount in the diet, but once adjustments had been made it began to rise again. In R.M. the amounts of Na and Cl in the diet were practically equivalent, /

equivalent, but the output of Cl was much less than Na, pointing again to some selective reabsorption of Cl. In the other two this was not so obvious, but they had some years since the operation in which to make any functional adjustments. Although no experiments were done with high Cl diets, the one test in J.C. where a Cl load was given showed an inability to get rid of excess Cl.

II B7. Plasma electrolytes during correction of acidosis.

Occasionally patients with ureteric transplants were admitted to hospital who had a marked acidosis and clinically were very ill, with vomiting, dehydration and weakness. When treated with the appropriate intravenous or oral salts, recovery was generally achieved within a few days. The blood electrolyte results in 9 patients before and after treatment are given in the Table II 4. W.A. was admitted on three different occasions, each time with a considerable hyperchloraemic acidosis, which responded rapidly with oral treatment. P.W. developed a chronic nephritis, but on three occasions I.V. sodium lactate was given, which resulted in a temporary relief of the hyperchloraemic acidosis. M.I. was admitted twice, but in her case symptoms were due to a very low serum potassium, and/

TABLE II 4. Plasma electrolyte changes on correction of acidosis.

Patient	Date	P.C.V. %	K _c	K _p	Na meq./l.	Cl	HCO ₃	B.U. mg./100 ml.	Treatment +
a) V.A.	25.2		2.8	*144	112	10	99	26.2 - 1.3	140 meq. Na) 36 meq. K) daily 1.3 - 4.3 48 meq. Na) 36 meq. K) daily 4.3 - 8.3 36 meq. K daily
	1.3		2.7	*144	100	21	68		
	4.3		3.5	*147	96	28	52		
	8.3		4.6	*150	104	22	52		
b)	11.8	40	4.2	140	115	9	89	12.8 - 16.8	148 meq. Na) 12 meq. K) daily 17.8 - 20.8 48 meq. Na) 54 meq. K) daily
	16.8		3.1	149	102	24	79		
	20.8	35	4.2	137	98	27	31		
c)	22.2	50	4.4	133	112	11	88	23.2	180 meq. Na 24.2 - 27.2 54 meq. K daily
	24.2	40	93	2.8	135	109	89		
	27.2	40	95	3.6	135	108	21	48	

+ K given as citrate and Na as bicarbonate orally unless otherwise stated.
I.V. Na given as lactate.

TABLE II 4. (Contd.)

Patient	Date	F.C.V. %	K ^c	K ^p	Na meq./l.	Cl	HCO ₃	B.U. mg./100 ml.	Treatment +
J.C.O	5.12	33	86	2.2	131	106	12	95	5.12 160 meq. Na } I.V. 26 meq. KCl }
	6.12	31	90	2.0	130	99	19	95	
	11.12	25	97	2.3	134	94	26	90	7.12 - 15.12 36 meq. K daily
	14.12	26	107	2.8	136	92	29	53	
	17.12	27	102	4.1	138	97	30	36	16.12 102 meq. K.
e)M.I.	20.4	36	-	2.7	138	103	26	72	21.4 - 4.5 50 meq. K daily.
	4.5	36	99	3.5	137	100	25	97	
	14.11	43	95	2.0	131	88	24	150	15.11 - 18.11 45 meq. KCl daily
b)	19.11.	34	102	3.4	131	98	22	100	
	21.11	33	96	4.1	135	102	21	85	19.11 - 21.11 18 meq. K daily
	26.4			3.9	148	116	6	160	26 and 27.4 270 meq. Na } I.V. 26 meq. KCl }
R.M.O	28.4	40	89	2.0	147	115	17	143	
	30.4	40	98	2.6	147	110	28	95	28 and 29.4 160 meq. Na } I.V. 52 meq. K }
	6.5	37	100	4.9	146	111	27	61	30.4 - 6.5 72 meq. K daily

TABLE II 4. (Contd.)

Patient	Date	P.C.V. %	Kc	Kp	Na meq./l.	Cl	HCO ₃	B.U. mg./100 ml.	Treatment
J.Q.o	21.4		2.2	129	115	-	215	21.4	
	22.4	37	81	1.6	135	109	150	167 meq. Na } 52 meq. KCl } I.V.	
	23.4	30	92	2.2	141	108	160	22.4	
	26.4	34	93	2.9	133	102	60	229 meq. Na } 78 meq. KCl } I.V.	
	28.4	34	102	4.5	133	102	67	24.4 - 25.4 48 meq. K daily 26.4 - 27.4 96 meq. K daily	
a) J.R.	21.6		1.9	*151	98	19	61	22.6 - 1.7	
	24.6		2.7	*151	101	20	46	50 meq. K daily	
	1.7		4.4	*155	110	18	31		
b)	22.11	35	97	4.4	133	109	44	23.11 - 26.11	
	26.11	37	97	5.6	136	102	61	48 meq. Na } 36 meq. K } daily	
C.T.	17.4		3.9	135	112	20	51	18 - 25.4	
	25.4		5.0	140	105	26	50	48 meq. Na } 36 meq. K } daily	

TABLE II 4. (Contd.)

Patient	Date	P.C.V. %	K _c	K _p	Na meq./l.	Cl meq./l.	HCO ₃	B.U. mg./100 ml.	Treatment +
a) P.W.	10.9	27	97	5.1	146	113	15	264	11 and 12.9 160 meq. Na I.V.
	13.9	30	97	4.0	151	112	22	240	
b)	19.9			4.4	147	116	11	435	20 and 21.9 160 meq. Na I.V.
	22.9	29	96	3.5	144	116	17	245	
c)	1.10	28	96	4.7	142	112	17	390	2 and 3.10 160 meq. Na I.V.
	4.10	29	104	3.6	142	99	22	550	
R.C.	1.2	46	91	2.1	146	107	12	132	80 meq. Na 27 meq. K

+ K given as citrate and Na as bicarbonate orally unless otherwise stated.
I.V. Na given as lactate.

o Complete balance data for these patients discussed in next paragraph (II B8).

and only a slight acidosis.

Two main points are evident from these 15 examples. The first is that in spite of the administration of considerable amounts of sodium, the plasma sodium levels did not alter to any great extent, even in some cases decreasing; the chloride and bicarbonate however, improved reciprocally by almost equivalent amounts. For example, J.C. received 160 meq. Na intravenously as lactate, and yet the plasma Na fell by 1 meq./l., while the Cl decreased and the bicarbonate increased both by 7 meq./l. Or, W.A. (a) receiving 140 meq. Na and 36 meq. K orally for three days showed an increase in bicarbonate of 11 meq./l., and decrease in Cl of 12 meq./l., while the Na remained the same. In 6 out of 9 instances for which figures are available, the P.C.V. fell, indicating that some expansion of the extracellular fluid had taken place, so that although the plasma Na appeared to remain the same, the actual amount in the E.C.F. had increased, and the Cl, although apparently decreased, may not necessarily have been very much less than originally.

The second important feature was that on correction of the acidosis, the plasma potassium fell in nearly every instance/

instance, by as much as 1 meq./l., in spite of administration of K. The only exceptions were J.R. and C.T., both of whom were receiving K, and who had the least degree of acidosis, and M.I. who was receiving K and did not have an acidosis. On 8 occasions the K was normal on admission, but in 5 after correction of the acidosis it fell markedly below normal, and required K administration before returning to normal levels (e.g. W.A. (b) and (c), R.M.), suggesting an incipient potassium deficiency. It is thus very important to recognise that in the presence of a marked acidosis, a considerable deficiency of potassium in the body may exist with apparently normal E.C.F. values.

Although some of the patients were treated satisfactorily with oral salts only, others were clinically very ill and dehydrated, necessitating immediate intravenous therapy. There is a limit to the rapidity with which K can be given intravenously, and generally not more than 1 g. KCl/ $\frac{1}{2}$ l. or pint of fluid is advocated, but latterly these patients were treated with 3 g. KCl/l. $\frac{1}{6}$ molar sodium lactate (\approx 39 meq. K) with 1 g. KCl/pint glucose as required, if the plasma K was very low (approximately 1 g. for every 0.5 meq./l. below 3.5 meq./l). The plasma K was checked daily/

daily until the acidosis was corrected, when the I.V. fluids were stopped, and if it was still below normal, as it frequently was, potassium citrate (30-70 meq. daily depending on the severity of the depletion) was given until it had been restored, usually by the end of the week. One patient (R.C.) died within 24 hours of admission and it was believed that K deficiency was one of the causes of death; nothing significant was found at the post mortem except for a slight pyelonephritis. The blood results on admission are shown at the bottom of the table obviously indicating a K deficiency with acidosis. He received $\frac{1}{2}$ litre sodium lactate intravenously containing 2 g. KCl (\approx 80 meq. Na, 27 meq. K), and in the 7 hours before death the rectal fluid was collected and found to contain 21 meq. K, 54 meq. Na and 45 meq. Cl, so that most of the K administered was lost. Assuming the lactate to have brought about a slight improvement in the acidosis or even an expansion of the E.C.F. only, the plasma K was probably even lower. Tissue analysis was carried out by Dr. Woodger; the muscle K was 73 meq./Kg. wet tissue as against his average normal value of 85 meq./Kg. wet tissue, so that this bears out the diagnosis. Cardiac muscle K was/

was however normal. Tissue analyses were also carried out in P.W. on autopsy specimens, but the results were actually high; the last electrolyte results before death showed a considerable acidosis (HCO_3^- 12 meq./l.), but the plasma K was normal and he had previously been getting potassium citrate. (See Table VI 4)

Figures are given in several instances of the blood cell potassium (K_c), but they did not prove very helpful. Thus in R.C., the patient with a very low plasma K and a proven tissue depletion, the K_c was only at the lower limit or normal. On the other hand in J.C. and J.Q. it was definitely below normal and in these instances did reflect a K deficiency, proven by the balance figures given in the next paragraph (Figures II 9 and 10). In the others it was normal, even in W.A. (c) who had a subclinical deficiency. The only assumption that one feels justified in making about tissue K as deduced from K_c , is that a low K_c in the presence of a low plasma K and an acidosis indicates a considerable body deficiency, and normal K_c does not necessarily preclude this. This whole question is discussed more fully in Section VI.

II B8./

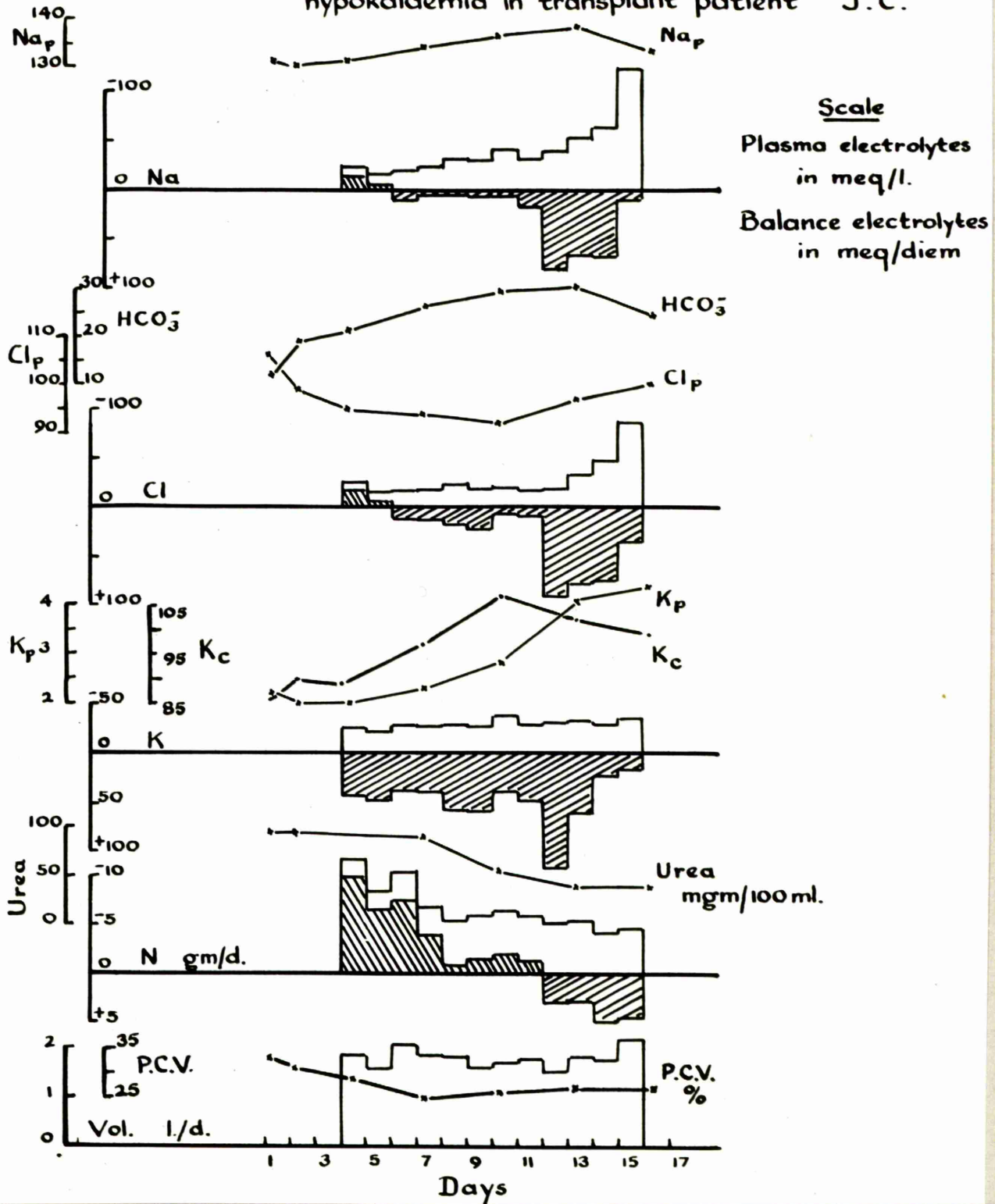
II B8. Electrolyte balance during correction of acidosis.

While observing changes in plasma potassium and the constancy of the plasma sodium during the cure of the acidosis, more detailed information of the movement of ions can only be obtained from the complete balance between intake and output. This was done in one patient J.C. and no further opportunity occurred until near the end of the period of study, when two further cases were admitted at the same time.

J.C. had had a ureterocolic transplant done at the age of 5 years, and now 20 years later was admitted for a plastics operation. However, she was very unwell, anaemic and undernourished, and her plasma electrolytes were estimated as a precautionary measure. She was found to have a very low plasma K of 2.2 meq./l., and a severe acidosis, but although the Cl was raised it was not extremely high as is sometimes observed in these patients; urea was also somewhat elevated. The hyperchloraemic acidosis was largely corrected within a day by I.V. sodium lactate, so that at the time of starting the balance, the Cl was normal, and the Na and HCO_3^- were only about 3 meq./l. below normal, whereas the K showed no improvement. The results/

results are shown in Figure II 9 and show several interesting features particularly with regard to potassium and nitrogen. To begin with, she was eating very little, so that her nitrogen intake was only about 2 g. In spite of this the N excretion was about 10 g./diem, so that there was a marked negative balance. The K intake in the diet was likewise very little, but in addition she was receiving 54 meq. potassium citrate/day during the whole period. In spite of some variations in the K intake, the urinary K was practically constant, so that for the entire period she was in positive balance, accumulating 590 meq. over the period of 12 days. After 6 days, half this amount had been retained, but the extracellular K had risen by less than 1 meq./l., so that it must have been soaked up into the tissues. It was about this time that the N output began to decrease and the blood urea was halved, so that the daily balance approached zero, and as the patient was now feeling and eating much better the intake increased so that for the last 4 days there was a positive balance. With still the same rate of retention of K, the E.C.F. K now rose by 1.5 meq./l. so that it was now back to normal. These results indicate that the tissue was markedly depleted of/

Fig II 9. Balance data showing correction of acidosis and hypokalaemia in transplant patient J.C.



of K, involving a corresponding amount of catabolism, and it was only after this had been replaced to a certain extent that tissue synthesis could be re-initiated. It appears that the tissues absorb K rapidly with little change in the extracellular levels until the cellular deficiency has been made good, and only then is the plasma K restored to normal. Of interest in this respect was the behaviour of the blood cell K. It was below normal at the beginning, but although it did demonstrate deficiency it did not indicate its magnitude. The plasma Na was slightly below normal, so the osmotic pressure would not be greatly disturbed, and the K_o would reflect this too. (For a discussion of this point see Section VI.) However, as K was retained it rose rapidly to a point actually above normal, and then proceeded to return to normal levels while the E.C.F. K also approached normal.

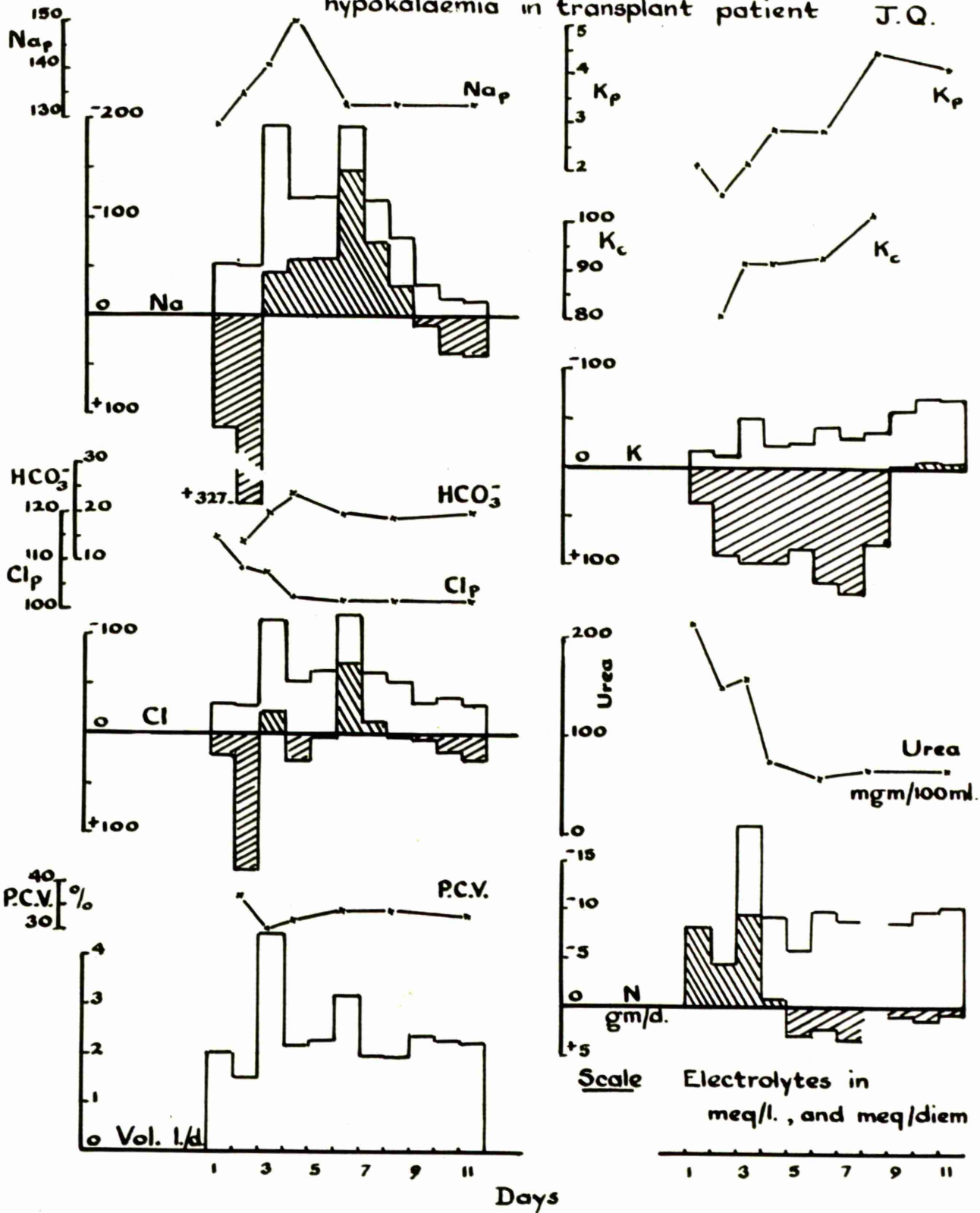
For the first days of the period, the Na and Cl balances were very slight and the intake was not great. The Na rose in the E.C.F. by 5 meq./l., and rough calculation (increase of 5 meq./l. in 10 l. E.C.F., less 20 meq. retained = 30 meq. from tissues.) shows that some of this came from the tissues, where it was presumably being/

being replaced by K; if anything there was also an
expansion of the E.C.F. at the time, so that even more
Na than is immediately apparent would now be circulating
in the E.C.F. It is more difficult to interpret Na and
Cl balances in terms of movements of ions between cells
and fluid, because any expansion or contraction of the
E.C.F. can easily account for anything up to 100 meq. or
more. The only guide we have here is the P.C.V., since
there were no other blood losses. There was a slight
positive Cl balance for the first half of the period, but
the plasma Cl continued to fall, while the HCO_3^- was
rising, so that in spite of the usual Cl retention, the
equilibrium was being altered. It should be noted too
that the HCO_3^- was increasing in the first 9 days before
the plasma K really rose much. This shift towards a
more alkaline pH would also encourage the passage of K into
the cells rather than the E.C.F. Once the patient was
taking a normal diet again there was a considerable retention
of Na and Cl, but after 4 days the output had increased
so that balance was being restored. The Cl had again begun
to rise and the HCO_3^- to fall, but were well within normal
limits. Another point to be mentioned is that while the
intake/

intake of Na and Cl were about the same the Na excretion nearly always exceeded the Cl, particularly latterly, giving additional evidence of the selective reabsorption of Cl.

Patient JQ. was admitted with all the symptoms of electrolyte imbalance - nausea, dehydration, weakness etc., and a severe hyperchloraemic acidosis with hypokalaemia was present. A balance was started immediately, although only I.V. fluids were given for the first 2 days, mainly sodium lactate and KCl. Analysis of the results shown on the chart (Figure II 10) indicate many similar features to J.C. A strongly positive K balance was present for over a week while K was being given, with comparatively small amounts in the urine; plasma K was slow to return to normal - 8 days and 650 meq. later - although K_c was normal by the third day, again showing how little reliability may be placed in K_c results in determining K deficiency. Like J.C. the N balance was negative to begin with, but the intake for the first 2 days was nil; after the third day it began to move nearer to zero, and was slightly positive for the rest of the period. Part of the negative balance of the first 3 days can be accounted for by the drop in blood/

Fig 110. Balance data showing correction of acidosis and hypokalaemia in transplant patient J.Q.



blood urea (the decrease of 140 mg./100 ml. equivalent to about 0.7 g.N/l. body water).

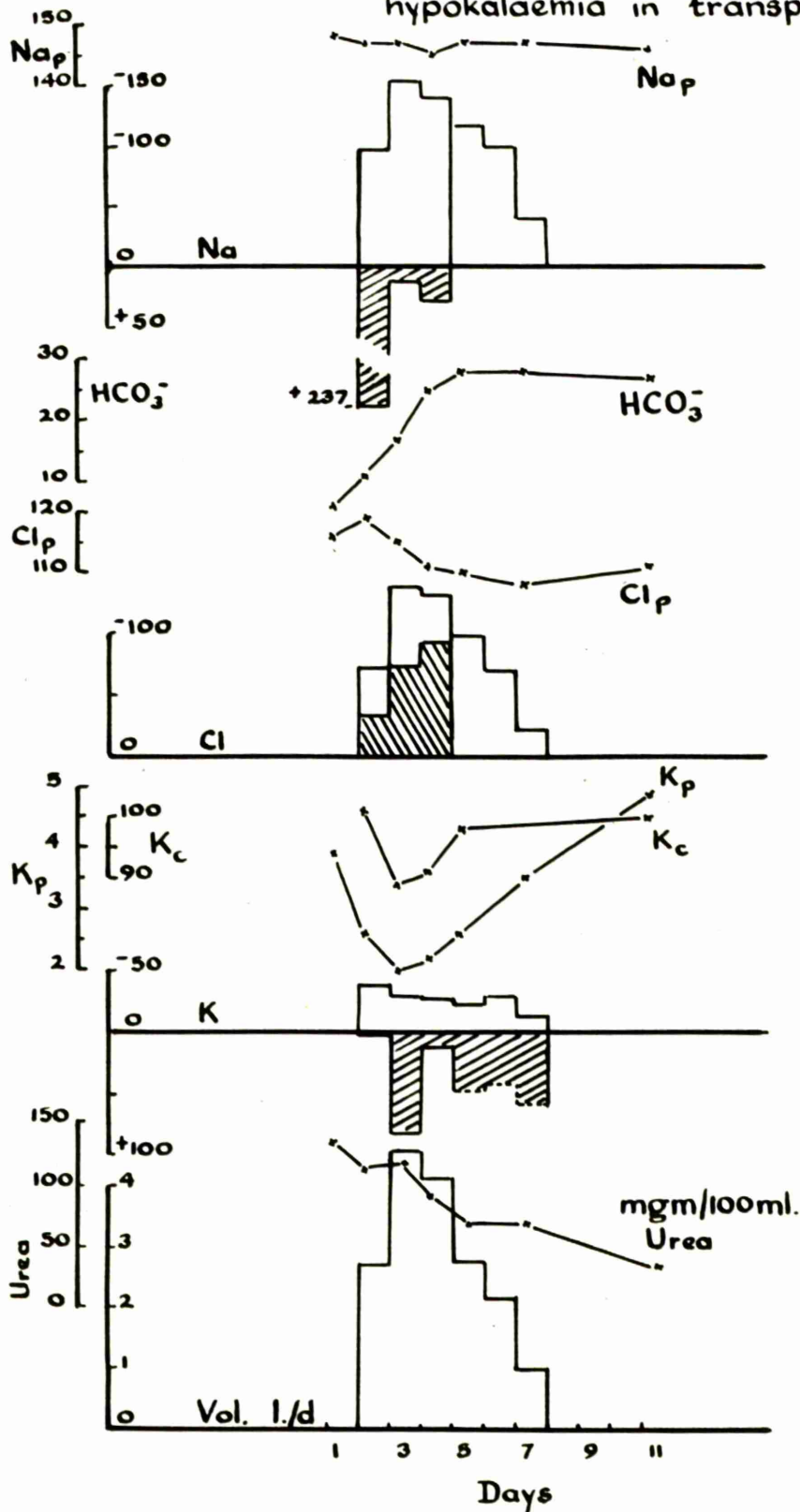
The Na and Cl balances were more difficult to interpret, because of the changes in fluid volumes. For example, on the second day the I.V. sodium administered was rather excessive and the output for that day unchanged, so that over 300 meq. were retained; but the fall of 7% in the P.C.V. showed that there had been considerable haemodilution, which if reflected by the whole extracellular compartment together with the actual increase in Na concentration would account for a large part of it. (11% x E.C.F. vol. 12 l. = 1.3 l. = 183 meq. Na + 6 meq./l. increase = 72 meq. Total 255 meq.)

The next day most of this excess Na and water in the E.C.F. was excreted, with a slight rise in the haematocrit and an increased concentration of Na in the plasma. For the next few days there was a strong negative balance, resulting at first in a fall in the E.C.F. Na, but then as this and the haematocrit remained steady, it presumably came from the tissues, having been displaced again by K. Similar consideration of E.C.F. volumes apply to the Cl balance, but here the curious fact is that in/

in spite of a marked improvement in the plasma levels there was no great overall loss of Cl. The bicarbonate acted reciprocally to the Cl as usual. Thus the administration of large amounts of potassium citrate over the period of a week resulted in a considerable uptake of K in the tissues, with some displacement of Na, restoration of protein anabolism, and maintenance of the improvement in the hyperchloraemic acidosis initiated by the I.V. sodium lactate therapy.

The patient R.M. was admitted a week after J.Q. with much the same symptoms. He had a much more severe hyperchloraemic acidosis, and on admission the plasma potassium was only at the lower limit of normal. It was not possible to do a full balance on him at the same time, but for the first 3 days he was only receiving intravenous fluids, so the balance is shown for these 3 days (Figure II 11). The acidosis had been largely corrected by then, and he was able to take food again, but in addition potassium citrate, 72 meq./day, were given. As with the others the most striking feature again was the marked fall of plasma K to half its original value on correction of the very considerable acidosis. At the beginning the amount of/

Fig II. Balance data showing correction of acidosis and hypokalaemia in transplant patient R.M.



Scale
 Plasma electrolytes
 in meq/l.
 Balance electrolytes
 in meq/diem

of K given orally just covered the amount excreted and was inadequate to maintain the E.C.F. levels when the tissues required it too; double the amount could have been given in this case, but as the plasma K originally was more or less normal, the extent of the deficiency was not immediately obvious. The plasma K only returned to normal after a week of K therapy. The K_c was normal on the second day, but then fell abruptly below normal when the plasma K was at its lowest point; one explanation of this could be that the red cells were acting as an emergency reservoir for K, as the tissues were calling for more K than was available in the E.C.F. The K_c however soon returned to normal before the plasma K did.

As in several of the cases mentioned, he received a large amount of I.V. sodium with a beneficial effect on the bicarbonate levels, but with no apparent effect on the E.C.F. Na. There was less alteration in the haematocrit too, so that its disappearance is unaccounted. A large amount of Na was excreted, although still less than the intake, and this was to a large extent neutralised in the urine by Cl, and as the Cl intake was very much less, 200 meq. Cl was lost in the first 3 days, as was apparent by/

by a drop of 10 meq./l. in the E.C.F. The urea which had been high when he was admitted also fell to normal as K was restored to the tissues.

SECTION II. ELECTROLYTE IMBALANCE IN PATIENTS WITH
URETERIC TRANSPLANTS.

II C. Discussion.

II C1. Incidence of biochemical abnormalities.

The results given here quite definitely confirm previous reports of hyperchloraemic acidosis in patients with ureterocolic transplants. The incidence of this in the Group I cases (those operated on before 1954) was 72% (29 out of 40), which compares with the figure of 79% given by Ferris & Odel (1950), but is higher than that reported in the B.A.U.S. Survey (1952), which was only 40%. A low serum K was also a more frequent occurrence than noted previously, being 55% here, only 35% in the B.A.U.S. Survey, and not mentioned by Ferris & Odel. But here these figures are compiled from repeat determinations in the same patients over a period of time, so that the chance of any transient abnormality occurring is probably greater.

II C2. Period of development of acidosis.

The hyperchloraemic acidosis may show itself any time after the first fortnight following operation. Thus 9% (3 out of 32) had developed the imbalance in a fortnight, and/

and 50% (8 out of 16) by the end of one month, but by the end of one year this had fallen to 33% (5 out of 15). Most patients showed some stabilisation after a few months, and frequently returned to normal, partly as a result of a restricted salt diet and alkali therapy, or some functional readjustment. Care et al. (1957) also found that after a time interval the reabsorption of Cl from the bowel was less than in the first month.

II C3. Electrolyte changes in the post-operative period.

In the immediate post-operative period, the acidosis and raised blood urea which frequently occurred are more likely to be due to the usual post-operative catabolism with insufficient renal clearance rather than a specific result of the operation; similarly with the low plasma K which also develops in this period, since intake is generally poor while losses are high, as was demonstrated in the balance experiments (Figures II 2, 3, 4). These balances also showed how small were the Na and Cl losses in the first few days following operation, except of course in the case where gastric contents were aspirated. Electrolyte therapy in the first one to two days following operation should therefore be at a minimum, calories being/

being the main requirement and water as necessary. Blood and gastric losses must of course be replaced quantitatively. There was a Na and Cl retention shown in all the balance experiments, probably because the intake was considerable while the fluid volume output was very small, combined with the well-known salt retention due to release of adrenal hormones under stress (Moore & Ball 1952). Although the intakes of Na and Cl were practically indentical, it was already noticeable that the amount of Na excreted was generally greater than Cl. There was also a negative K balance post-operatively due to the very low intake and relatively high concentration of K in the rectal fluid. Where fluid output is high, and oral intake of food still poor, extra K may need to be given after the first five or six days.

The balance experiments in these patients were not carried on sufficiently long enough time to show the actual development of the imbalance, since the time of onset could not be predicted. From blood results alone done in the same patient over a period of time, the hyperchloraemia generally appeared simultaneously with the acidosis, but the hypokalaemia seemed to develop independantly. Na was/

was normal nearly all the time.

II C4. Effect of alterations in diet, acid and alkali load.

The balance experiments in Section II B6 were designed to show the effect of varying intake on the blood levels. On a low NaCl diet three of the four patients showed a reasonable adjustment. In J.Q. (Figure II 5) there was little net gain or loss of these ions but there was a definite improvement in the blood levels. In R.M. (Figure II 7) on the other hand, no adjustments were made and there was a large negative Na and Cl balance, but without any apparent change in the E.C.F. Levels.

An acid and an alkali load were given in two instances. A dose of NH_4Cl resulted in a retention of Cl and increased plasma Ca, which however returned to normal a few days later although the extra Cl had not been lost. The acid load had little effect on either Na or K plasma or urine levels, though if anything there was a very slight increase in plasma K (Figure II 8). Sodium lactate, on the other hand, brought about a dramatic improvement in the plasma Cl and HCO_3^- in R.M. (Figure II 7), but with no increase in Cl excretion, and in spite of the large amount of Na retained, the plasma Na fell. Also there was/

was no change in K excretion, but plasma K fell by over 1 meq./l.

These examples serve to point out the inadequacy of blood levels alone in defining any situation. Thus changes in net balance of Na occurred in Figures II 7 and 11, which were not reflected by changes in E.C.F. concentration, while in Figures II 5, and 9 there was a considerable difference in plasma levels without corresponding changes in the overall balance. In other words, there must have been ionic exchanges between the fluid compartments and/or changes in volume of these fluids.

II C5. Alterations in electrolyte distribution during treatment.

Ionic and volume changes were also shown to occur in patients who had developed a marked electrolyte imbalance and clinically were very ill. Administration of large amounts of Na did not always result in much change in plasma Na, but brought about a marked improvement in the acidosis and hyperchloraemia, while K became subnormal. Where balances were done, the lowered plasma Cl was not necessarily due to a negative Cl balance (e.g. Figure II 9 and 10) and the stationary Na could be in the face of considerable/

considerable Na retention (Figure II 11). The only indication here of E.C.F. volume was the P.C.V., and necessarily rough calculations based on this suggested that the excess Na was largely accommodated by an expansion of the E.C.F., which was also sufficient to account for the lowered Cl by dilution. The improvement in acid-base balance was however maintained and the patients felt much better. On other occasions of course, the blood levels did reflect the balance (e.g., Na in Figure II 10, Cl in Figure II 11).

While most people are agreed on the alkali therapy required by these patients, actual electrolyte balances have rarely been done, and this point does not seem to have been appreciated. Kekwick et al. (1951) showed a positive Cl retention in four patients with ureterocaecostomies, but otherwise very few figures for balances, particularly K, have been given in the literature, although the rectal fluid has been analysed on a few occasions. Pines & Mudge (1951) describing three cases of renal tubular acidosis, (one of whom had had a ureterosigmoidostomy, and therefore not strictly comparable to the others) gave figures for a three day balance during treatment/

treatment in that patient, showing a positive K balance, and a slightly positive Cl balance with a decrease in plasma Cl, but these points were not emphasised very much.

II C6. Development of hypokalaemia.

The other important factor which does not seem to have been sufficiently emphasised is the development of hypokalaemia. Ferris & Odel (1950) in their original paper make no mention of this, nor did Doroshov (1951), while Lapidus (1951) mentions that it is normal. Persons et al. (1952) remarks that it tended to be low but only Wilkinson (1952) and Jacobs & Stirling (1952) give any significant figures. In the patients discussed here, many had a low plasma K in the immediate post-operative period, although as pointed out previously this was probably due to the usual post-operative catabolism with inadequate replacement; however, 55% of the long-standing transplants also had a low K, a figure which cannot be ignored. One reason for overlooking this K deficiency previously is that a normal or only slightly subnormal plasma K may be present while there is a considerable tissue deficiency, particularly if there is also a marked acidosis. Thus all three patients with a normal plasma K and acidosis on admission showed signs/

signs of K deficiency and a low plasma K once the acidosis was corrected. The balance data demonstrate the extent of the deficiency: J.C. (Figure II 9) retained 490 meq. and J.Q. (Figure II 10) 650 meq. before the plasma level returned to normal, while R.M. (Figure II 11) admitted with a plasma K of 319 meq./l., had a plasma K of 2.0 meq./l. after the acidosis was corrected, which required over 250 meq. before it was brought back to normal. A similar effect was observed with J.Q. (Figure II 5).

This potassium must have gone into the cells almost entirely, since the amount in the E.C.F. is very small by comparison. Evidence for displacement of Na from the cells by K was found in Figures II 5 and 9, where the increase in plasma Na was not due to a positive balance or haemoconcentration. In both cases there was a gradual improvement in the acidosis concomitantly.

The lowering of the plasma K was not due to increased excretion of that ion as a result of the relative alkalosis (i.e. correction of long-standing acidosis). In fact it was remarkable how little the K excretion was affected by the various conditions. Thus there was a constant appreciable loss of K in the rectal fluid even when the body/

body was obviously deficient and there was a demand for K. (Figures II 9, 10, 11 and patient R.O. Table II 5), and R.M. (Figure II 7) was definitely unable to adjust to a low K intake and was in negative balance until this was increased. Doubling the K intake had little effect on K excretion in Figures II 7, 9 and 11, and as mentioned before there was little change when acid or alkali loads were given. In other words, control of K excretion did not seem to be very effective in these patients.

The question of the influence of acid-base balance on K metabolism has been the subject of a considerable amount of work. Hypokalaemia has been shown to occur repeatedly with a metabolic alkalosis, and hyperkalaemia with an acidosis e.g., in uraemic coma. But it is now recognised that plasma K is an unreliable index of body K and it may be high, normal or low in K deficiency, depending on the circumstances (Darrow 1945, Fourman 1952, Moore & Ball 1952). Quantitatively of course it only requires a very small change in cellular K, which may be undetected when estimated, to make a very large difference to plasma and urine K. Breakdown of cellular material liberates K e.g. in starvation and dehydration (Atchley et al. 1933, McCance 1937, /

McCance 1937, Elkinton & Taffel 1942) and renal secretion is increased (Mudge, Foulks & Gilman 1950), but this only as long as renal function is efficient.

When considering K metabolism, the integrity of the kidneys is an important factor. If renal function is impaired, K conservation is limited, and if urinary volume is high as in chronic nephritics, considerable losses may occur (Burrows, Commons & Burnett 1949); on the other hand if the patient is oliguric and unable to excrete K, a high plasma K will result (Hoff, Smith & Winkler 1941, Bywaters 1944). Finally a long-standing K deficiency from other causes may lead to permanent damage to the kidney (Schwarz & Relman 1953).

These factors may all play their part in the K deficiency of these patients. The urine volume is generally large, possibly partly due to the osmotic effect of the extra Cl load, and the K concentration is always appreciable, possibly as a result of secretion by the bowel. This could lead to a deficiency which in turn may affect the ability of the kidneys to control acidification (Schwarz & Relman 1953, Clarke et al. 1955). On the other hand, K conservation is limited in the presence of acidosis (Fourman 1952)./

(Fournier 1952). In addition renal function in these patients is not always 100%, and may for example be affected by back pressure and infection, and this also may impair the ability to conserve K and control the acidosis. This however is probably the precipitating rather than the causative factor.

The acidosis will also help to mask the deficiency as it will tend to prevent K going into the cells (Scribner, Fremont-Smith & Burnell 1955) and will therefore help to maintain the plasma levels. It has been suggested that hypokalaemia in the presence of acidosis indicates a more severe depletion than in alkalosis (Guest 1942, Nichols & Nichols 1953). On correction of the acidosis there is an immediate demand by the tissues for K, which may lead to a very low plasma K, even to fatal limits, unless adequate precautions are taken.

As far as the hyperchloraemic acidosis is concerned, the evidence here supports the finding of chronic Cl retention, possibly by a Cl/HCO_3^- shift in the colon, since the two are nearly always balanced in blood (Figure II 1), and the rectal fluid is always alkaline. An alternative hypothesis/

hypothesis which would fit these facts is the primary reabsorption of hydrogen ion in the bowel (possibly as NH_4^+), with chloride going along with it to maintain electrical neutrality. However, the chloride reabsorption is not entirely dependant on concomitant H^+ movements as chloride was reabsorbed from saline solutions (Goldschmidt & Dayton 1919, Annis & Alexander 1952) while Bohne & Rupe (1953) found it was reabsorbed more quickly from isotonic saline than from isotonic ammonium chloride.

Unfortunately no direct evidence of H^+ reabsorption or increased bicarbonate excretion was available because of bacterial decomposition and strong alkalinity of the rectal fluid, and similar considerations apply to urea and ammonia estimations.

While a degree of biochemical imbalance appears to be inevitable in these patients as a result of their operation, it can be alleviated by treatment with alkaline Na and K salts, and moderation of the Cl intake. The patients appear to adjust themselves to the altered circumstances and may report for years with a considerable acidosis without any clinical symptoms other than a degree of thirst. The trouble arises when something happens to upset/

upset this precarious balance, for example, a slight infection or sickness, and the kidneys are unable to deal with the additional load from extra catabolism. Then it is essential that a close check should be kept. Given attention to these points, there is no reason why these patients with ureteric transplants should suffer from the biochemical effects of their operation.

SECTION III. ELECTROLYTE CHANGES IN ACUTE RENAL

FAILURE AND ANURIA.

III A. Introduction.

III A1. Retention of nitrogenous and acidic metabolites.

The changes that occur in acute renal failure have been reviewed by Swan & Merrill (1953) and Bull (1955 a & b) amongst others. The most obvious abnormalities in the blood constituents are the increase in nitrogenous and acidic products with decrease in bicarbonate concentration. The increases in urea, and in some instances creatinine and uric acid, are frequently employed as indices of the progress of the disease. The variations in plasma inorganic phosphorus do not seem to have been used to the same extent, although its increase in renal disease was noted as long ago as 1923 (Denis & Hobson). This was one of the lines of investigation in these patients.

III A2. Changes in serum magnesium.

The importance of serum magnesium in renal failure has not been entirely settled, as relatively little work has been done on the subject. For this reason the general review of magnesium metabolism was undertaken (See Section V). It has been reported as being high in uraemia (Watchorn & McCance/

McCance 1932, Brookfield 1937), and drowsiness, similar to that of uremic coma has been produced experimentally by the administration of Mg and also clinically when given as a purgative to chronic nephritics (Hirschfelder 1934). Serum magnesium estimations were therefore done whenever possible in these patients.

III A3. Changes in other electrolytes.

The electrolyte which is known to have a definite toxic effect is potassium, (Bywaters 1944, Keith & Burchell 1949, Bull 1953). Winkler, Hoff & Smith (1938) gave intravenous KCl to dogs and noticed characteristic changes in the E.C.G. until death occurred at plasma K levels of about 14 meq./l. Later (Hoff, Smith & Winkler 1941) they showed that there were similar changes in plasma K and E.C.G. in dogs made anuric by nephrectomy or ligation of the ureters. They found that the plasma K and E.C.G. changes were not so pronounced in chronic nephritics, but then these patients generally had a reasonably good urinary volume and were able to excrete sufficient potassium to prevent a toxic rise. The plasma potassium may in fact be low in these patients owing to continued urinary losses and inadequate replacement

(Burrows/

(Burrows et al. 1949, and Schoch 1951).

In the diuretic phase of recovery from anuria, renal function is still poor so that there are some similarities then to the chronic nephritic. Thus there is a large volume of urine, of fixed specific gravity, the ability to form ammonia is impaired and conservation of base is inadequate. (Marshall 1949, Platt 1950, Iseri et al. 1952, Brod 1956), so that potassium and sodium deficiency may develop. Plasma sodium and chloride are also frequently below normal while the patient is anuric, but as there are no losses from the urine, it is more likely to be a redistribution rather than a deficiency. Also there is very often some haemodilution, partly from water produced by catabolism, but also from administration of fluids in excess of losses.

III A4. Treatment of anuric patients.

The fluid balance must be carefully controlled in anuric patients and the minimum amount of fluid given to prevent overhydration (Peters et al. 1929, Bull 1955 b, and Merrill 1955). It is also necessary to withhold salts other than those required for extra-renal losses, and in some cases where plasma K is at a dangerous level it may be/

be lowered temporarily by giving intravenous glucose and insulin, or with ion exchange resins (Bull et al. 1953, Evans & Milne 1953). It is also essential to give sufficient calories so that body protein is not used for ordinary energy requirements and accumulation of breakdown products is thereby minimised. Where fluid intake has to be kept at a minimum this is a matter of some difficulty, but can be done with intragastric peanut oil, or intracecal 40% glucose (Bull 1952).

III A5. Use of anabolic steroids.

With the advent of anabolic steroids, it was suggested that this catabolism could be further suppressed.

Kochakian (1946) gives a good review of the comparative anabolic efficacy of the various forms, methyl testosterone heading the list for potency, 17-methyl androstenediol having two-thirds of its activity; positive nitrogen, sodium, potassium, phosphorus and water balances were obtained. Butler, Talbot & MacLachlan (1942) briefly mention that testosterone lowered plasma K levels, without altering muscle activity, E.C.G. or sugar levels, while giving a positive potassium and nitrogen balance. Klopp et al. (1945) gave testosterone to 4 normal subjects and

5/

5 patients with renal impairment, and found no difference in G.F.R., R.B.F. or maximum tubular reabsorption of glucose, so that its effect was not so much on renal function as on cell metabolism; renal mass however does increase when the steroid is given over a period of time. With these results in mind, anabolic steroids were given to some of the patients here, to see if it alleviated their condition.

SECTION III. ELECTROLYTE CHANGES IN ACUTE RENAL FAILURE AND ANURIA.

III B. Results.

III B1. General changes in plasma electrolytes.

Plasma electrolyte results are presented from 14 patients with anuria (Table III 1 a,b, Figures III 1,2 and 3). Half were admitted with anaemia and anuria, in the others it developed following operation. Nephrostomies were performed in four cases with relief of the obstruction in two.

All the usual abnormalities were present in some degree. As was to be expected, the most obvious were the retention of nitrogenous and acidic products, as shown by the raised urea, phosphorus, and lowered bicarbonate. The bicarbonate was below normal in all, with one exception (C. McI.), but markedly depressed (less than 16 meq./l.) in only four.

Of the cations, plasma K was above normal in 12 of the 14 patients but above 7 meq./l. in only 4. Blood cell potassium (K_c) was estimated at the same time in 12 patients and was below normal in 7 of these. In 3, the low K_c was present with a marked acidosis, high plasma K and/

TABLE III 1. Plasma electrolytes in patients with oliguria or anuria.
III (a) Patients recovered.

Patient	Day after onset of anuria.	P.C.V. %	K _c	K _p	Na	Cl	HCO ₃ ⁻ meq./l.	Ca Mg	Urea mg./100 ml.	P	Remarks
1.M.C.	4	-	-	7.4	146	101	9	-	264	10.0	Diuresis
	5	17	87	6.1	145	101	10	-	188	10.1	5th day.
	6	18	97	5.2	136	97	11	-	268	10.3	
	11	24	-	3.4	134	88	19	-	216	4.5	
2.W.L.	4	34	99	5.3	126	91	19	4.5	2.2	6.3	Nephrectomy
	5	34	90	4.0	123	93	17	5.0	2.7	5.1	Diuresis
	9	32	-	4.0	134	100	22	4.9	2.1	4.1	4th day.
	11	32	91	3.5	142	101	24	4.5	1.9	-	
3.H.R.	3	38	89	7.6	134	98	16	5.2	3.6	7.2	Calculus
	5	34	90	4.5	136	101	19	5.2	3.1	5.5	obstruction. Nephrostomy 3rd day.
4.D.S.	5	-	-	4.5	128	87	21	4.9	2.2	6.1	Ileocysto:
	6	-	-	4.3	123	87	16	4.6	2.2	5.9	:plasty.
	8	32	89	4.4	122	77	20	4.7	1.99	7.7	Nephrostomy
	10	36	85	4.0	120	79	22	3.8	2.2	8.0	5th day, not
	12	34	86	3.8	129	87	23	4.1	2.5	7.2	draining well
15	27	98	4.6	132	99	21	5.1	2.0	4.2	until 10th day.	

TABLE III (c) Two patients with oliguria following chronic nephritis.

Patient	Date	P.C.V. %	K _c	K _p	Na meq./l.	Cl meq./l.	HCO ₃	Ca	Mg	Urea mg./100 ml.	P	Remarks
J.G.	16.7	-	-	4.1	133	90	21	-	-	365	9.9	Polycystic kidneys.
	19.7	19	94	4.8	133	94	19	3.9	3.1	340	11.8	
	24.7	17	92	4.7	124	84	17	-	3.8	425	9.1	Durabolin
	31.7	-	-	4.3	134	87	15	-	-	580	13.5	Died 6.8.
P.W.	10.9	27	97	5.1	156	113	15	-	-	264	-	Transplant
	13.9	30	97	4.0	161	112	22	-	-	240	-	7 months ago.
	19.9	-	-	4.4	147	116	11	-	-	435	5.5	I.V. Na lactate
	22.9	29	96	3.5	144	116	17	-	-	245	3.9	12.9 and 21.9
	29.9	28	96	4.3	145	114	17	5.3	2.2	405	4.2	
	16.10	28	103	3.4	143	106	17	5.0	2.1	570	7.2	Died.

Fig III Ia Plasma electrolytes in patient E.R. with anuria.

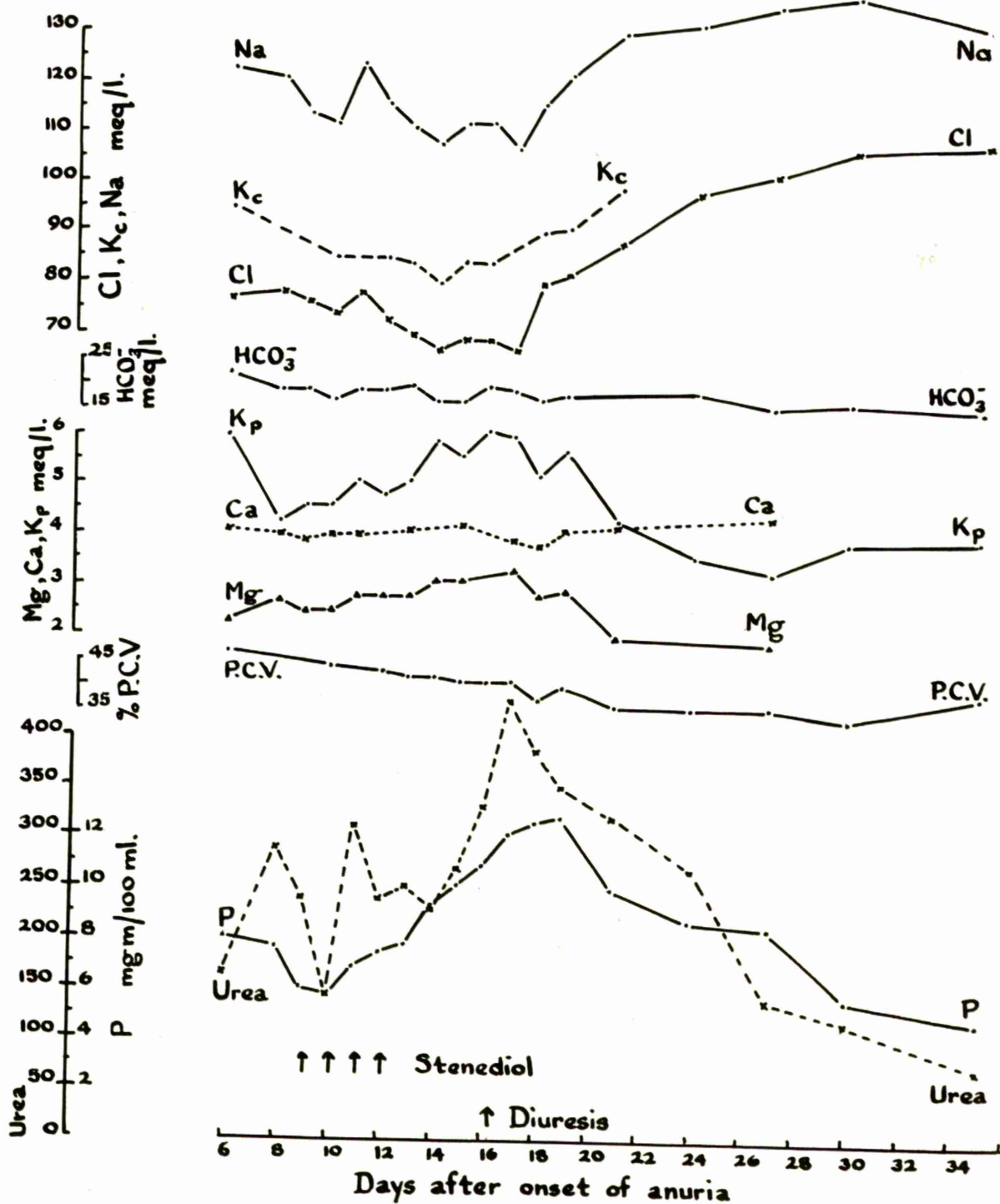


Fig III 1b

Urine electrolytes in patient E.R. with anuria.

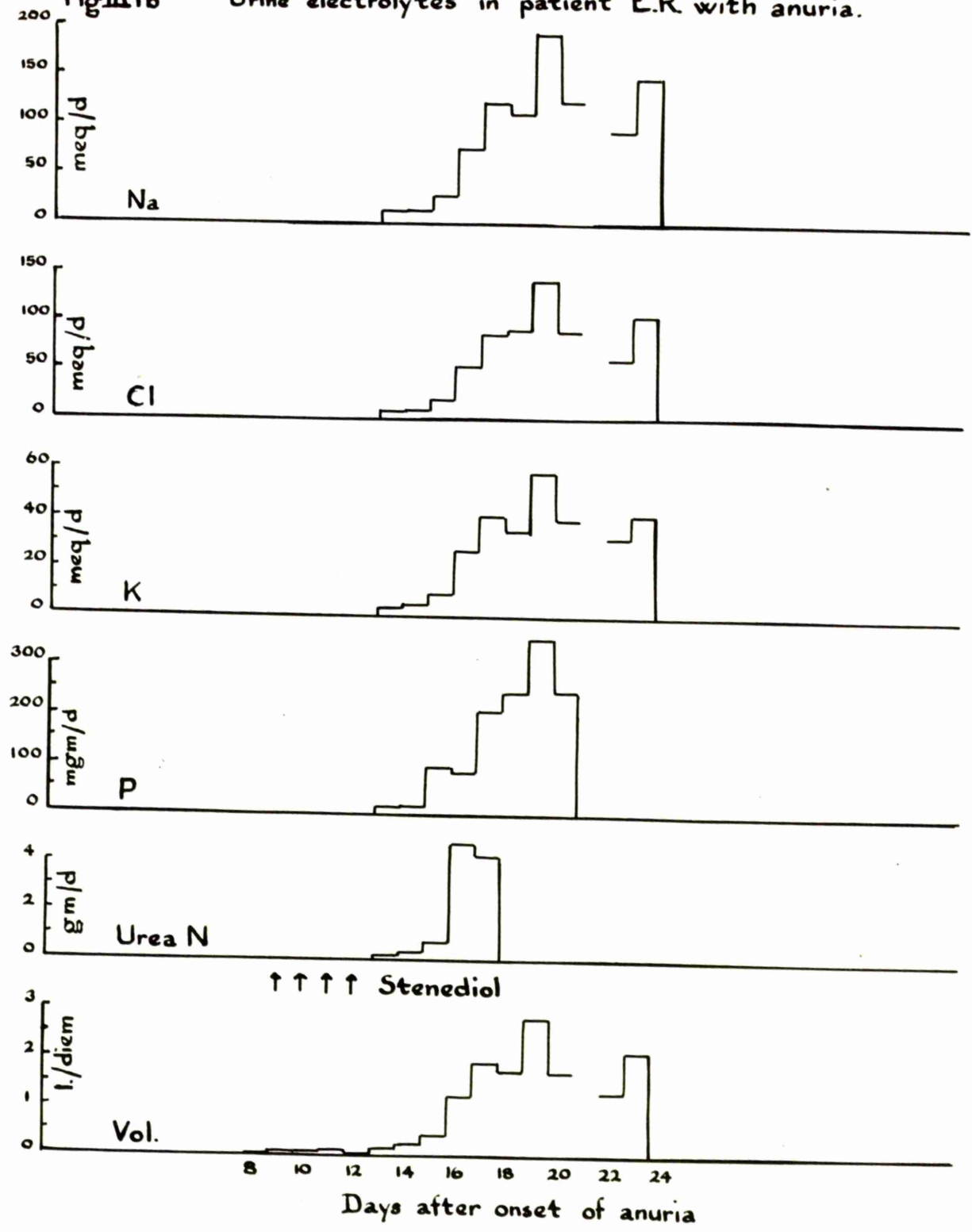


Fig. III 2 Plasma electrolytes in patient C.D. with anuria.

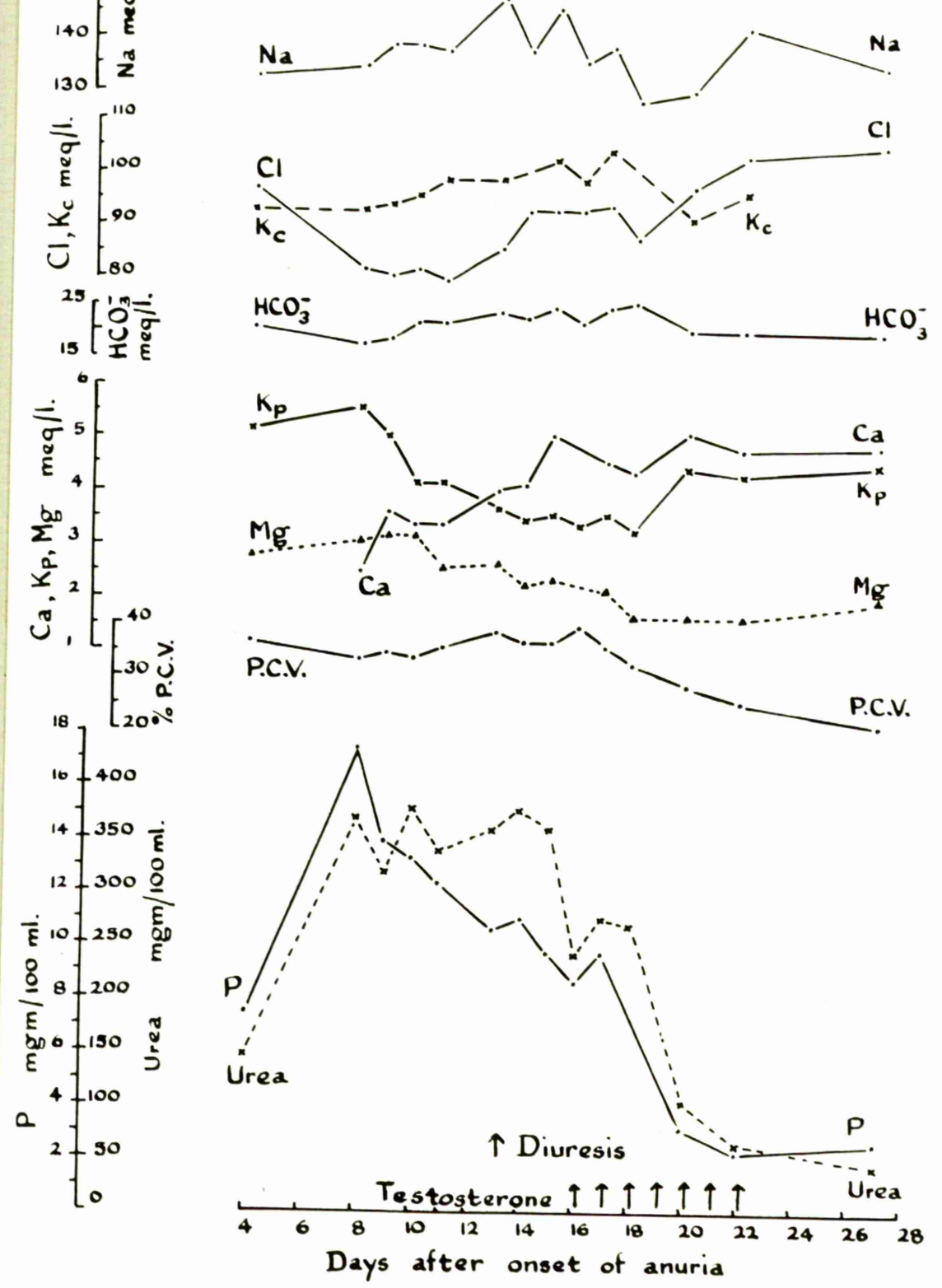
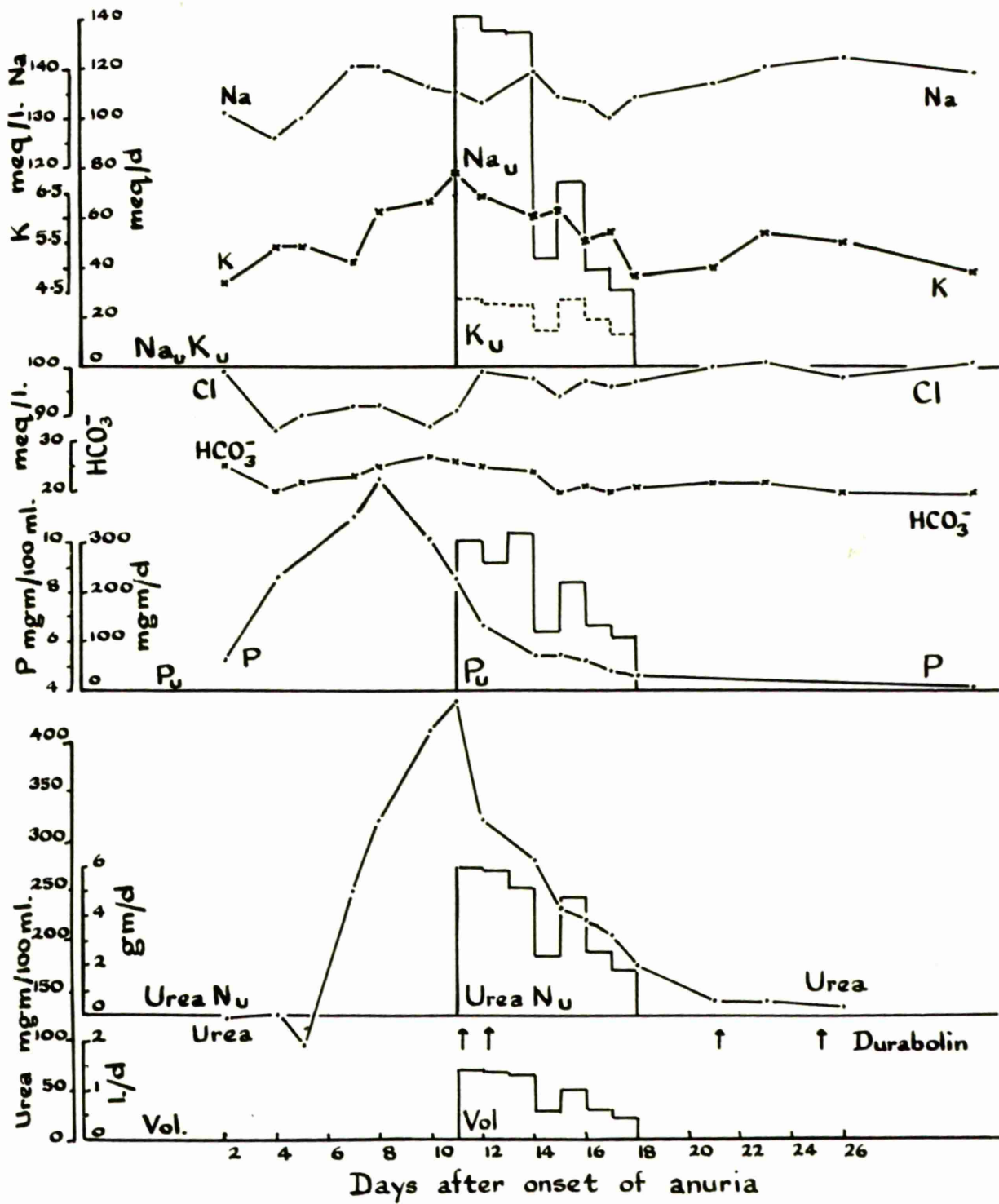


Fig III 3 Plasma and urine electrolytes in patient C.M. with anuria.



and normal Na. In two others there was hypotonicity as reflected by the plasma Na, with normal plasma K and no great disturbance of the acid-base balance; in the remaining two there was both acidosis and hypotonicity. In three of the four with normal plasma K there was minimal disturbance of acid-base equilibrium and tonicity; in the fourth patient (C.McI.) it was above normal, but this patient had a metabolic alkalosis before development of renal failure and plasma K was below normal at this point. For further discussion of changes in K_o levels, see Section VI.

Plasma magnesium was estimated in most of these patients and was above normal in all except two. In general it was raised when the plasma K was also increased but not always to the same extent and not in every case (e.g., R.N. Table III 1b, J.G. Table III 1c.) Calcium was below normal in 7 of 9 cases in which it was done, all of these having high P levels; P was only moderately raised (up to 7.2 mg./100 ml.) in the two with normal Ca.

The patient C. McI. mentioned above is particularly interesting as he developed a metabolic alkalosis caused by vomiting due to intestinal obstruction following transplantation/

transplantation of the ureters. Finally renal failure developed so that he had a renal acidosis superimposed on a metabolic alkalosis, and an apparently normal bicarbonate. P was normal during the alkalosis although the urea was raised, but began to rise when the kidneys began to fail. Magnesium likewise increased at this point.

III B2. Plasma electrolytes in two patients with chronic uraemia.

Two other patients (Table III 1c) although not completely anuric developed oliguria after chronic uraemia, so may also be discussed here. J.G. had an operation for polycystic kidneys, and P.W. had chronic nephritis some months after a ureteric transplant. Both had very high urea levels for some time, but there was no obvious disturbance of K distribution in the blood, both plasma and cell K being normal, even low occasionally in P.W. J.G. had the typical moderate acidosis, high P and Mg, and lowered Cl. P.W. is not strictly comparable as his acidosis was due partly to the altered urine pathway, with retention of Cl. Slight temporary improvement in the hyperchloraemic acidosis was obtained by/

by giving intravenous sodium lactate, but it relapsed in a day or so. It was also noticed in this case that Mg was normal the whole time, and P was never greatly increased even towards the end.

III B3. Plasma inorganic phosphorus as an indication of clinical condition.

A comparison of the plasma urea and P results in these patients is revealing. Although on the whole they moved in parallel this was not always so and they did not reach the same relative heights together. For example, in C.B., J.F. and W.S. (Table III 1b) the urea was less than 200 mg./100 ml. but the P was greater than 10 mg./100 ml.; these patients all died. On the other hand, in W.L. and H.R. (Table III 1a) the urea was greater than 200 mg./100 ml. but the P was less than 7 mg./100 ml., and these two survived.

The change in urea and P levels is also significant: for example, in R.N. (Table III 1b) the urea was steady at 305-296 mg./100 ml. while the P rose from 9.3 to 11.6 mg./100 ml., which indicated the continuing clinical deterioration. On again, in C.D. (Figure III 2) the urea in seven days showed little change, from 372-360 mg./100 ml./

mg./100 ml., and in the same time the P fell by nearly half, 17.4 - 9.7 mg./100 ml., and this again compared with the improved clinical condition. In C.M.

(Figure III 3) and H.R. (Table III 1a) the urea increased 320 - 440 and 189 - 212 mg./100 ml. respectively, but the P was decreased from 12.7 - 8.5 and 7.2 - 5.5 mg./100 ml., and again the latter gave the truer indication of the clinical picture. Although the P returned to normal some days before the urea, the fact that the urea remained elevated indicated that recovery was not absolute.

From these few results it appears that in acute renal damage a moderately raised urea with a very high P carries a considerably graver prognosis with it than a urea at the same level with only a slightly elevated P, but should the P begin to fall although the urea remains at the same level there is hope that the recovery period has set in.

P.W. with chronic nephritis was one exception to this, as in spite of persistently high urea levels (over 400 mg./100 ml. for 10 days) the P fluctuated around 4 - 7 mg./100 ml., but it was only latterly that he developed oliguria. In C.McI. the P only rose terminally to 9 mg./100 ml./

mg./100 ml. although the urea was over 300mg./100 ml., but in his case the preceding alkalosis may have prevented it rising to the same extent.

The plasma bicarbonate on the whole moved in parallel with the P rather than urea, as might be expected from the indications of increased acidosis.

III B4. Effect of anabolic steroids.

Anabolic steroids were given to five of the above patients with varying degrees of success. Stenediol (methylandrostenediol) was given to E.R. (Figure III 1a and b) for 5 days after 9 days anuria, but was stopped as she began to develop an intracellular oedema. After the first dose, plasma P, urea, Na and Cl all fell, but it cannot be said for certain that this was the effect of the steroid as it merely continued the trend from the previous day. Nevertheless, for the remaining four days on the drug, these did not get much worse and it was only when four days later she started to produce over 1 litre urine that the P, urea, K and Mg all reached their highest levels. It seems possible then that the steroid had prevented these substances from passing out of the cells into the extracellular fluid during the critical period of/

of anuria, and in this way may have contributed to the successful recovery of the patient.

Testosterone was given to two patients, C.D. and R.N., both of whom developed anuria following operation, C.D. after a nephrectomy and R.N. after a prostatectomy. In C.D. (Figure III 2) the anuric phase was actually over, and the drug although producing a very considerable drop in P, urea and Mg after a day's time lag, was again continuing the trend of the previous day. With her as in C.D., there was also a fall in plasma Na and haematocrit. With R.N. (Table III 1b) on the other hand although it brought about a transient fall in plasma K, the urea continued to rise, and the patient died the following day.

Durabolin (19-nortestosterone - 17-phenylpropionate) was given to two other patients, C.M. and J.G. J.G. (Table III 1c) was the one with polycystic kidneys, though not actually anuric. The steroid had no appreciable beneficial effect apart from a temporary halt to the rise of urea and the patients condition gradually deteriorated. In C.M. (Figure III 3) the steroid was given during the diuretic phase, and the following day there was a marked drop in urea, a slight fall in K and Na, while P continued its/

its declination. Ten days later it was given again as the urea was remaining stationary at 140 mg./100 ml., but the steroid did not affect it this time.

III B5. Urine electrolytes in the diuretic phase.

Urine electrolytes were estimated only in two patients, E.R. and C.M. (Figures III 1b and III 3). In E.R. the considerable diuresis was accompanied by large losses of Na, Cl and K, coincident with an increased concentration of Na and Cl in the E.C.F. This was not just a result of haemoconcentration as might be expected, since according to the haematocrit the E.C.F. was still expanding. This suggests that a considerable amount of water, Na and Cl had been retained in the tissues, possibly as a result of the stenediol administration. Certainly an intracellular oedema developed during treatment with the stenediol. It was three days after treatment was stopped that diuresis began. Plasma K fell below normal during the diuretic phase as a result of the demands made by tissues and K_c coupled with increased urinary loss.

In C.M. the immediate Na losses did not have a very great effect on the plasma Na, but plasma K again fell below normal, although losses in the urine were not so marked.

SECTION III. ELECTROLYTE CHANGES IN ACUTE RENAL FAILURE AND ANURIA.

III C. Discussion.

III C1. Variations in plasma phosphorus and urea levels.

The patients with renal failure studied here all showed the typical changes in blood composition, i.e., increased urea, plasma K, P, Mg, and decreased bicarbonate, Na, Cl, Ca and cell K. The levels varied greatly e.g., urea was as high as 580 mg./100 ml., P was up to 18 mg./100 ml., and bicarbonate in one case was as low as 2 meq./l. The rate of change of the various ions was very different in some patients, and they did not always alter simultaneously. This was particularly striking with regard to urea and P. A moderately raised urea (up to 200 mg./100 ml.) with a relatively high P (more than 10 mg./100 ml.) appeared to indicate a more severe lesion than a much higher figure for urea with a P less than 8 mg./100 ml. Although on the whole they tended to rise in parallel, on several occasions the steady rise or fall of P gave a truer indication of the patients clinical condition than the urea levels, which were subject to more fluctuation.

The/

The mechanism behind this is more difficult to explain. The N/P ratio in tissues is normally 14.7/1 (Albright & Reifenstein 1948), so that when tissue is breaking down, for each mg./100 ml. rise in P, the urea could theoretically rise by approximately 30 mg./100 ml. This does not always hold in practice, as although most of the protein probably goes to urea, some will remain as amino-acids, and creatinine, uric acid etc., are also formed. Some of the P will be absorbed by bone, as witness the concomitant fall in Ca, and some will be retained as organic esters within the cell. If the plasma P does not increase very much while the patient is anuric and the urea is rising, it suggests that although protein breakdown is in progress, possibly as a result of energy requirements, the other body processes are functioning sufficiently to be able to compensate partially, and organic phosphate esters are still being formed. This could explain the fall in P in patient C.D. while she was still anuric while the urea fluctuated at a high level. On the other hand, if sudden severe general catabolism takes place, the P will tend to accumulate as inorganic P with little ester formation, before the urea reaches very high/

high levels. Support for this theory lies in the fact that generally the bicarbonate was lower in these cases, indicating a more severe degree of acidosis, but further work is required to confirm this. This total rather than partial catabolic phase would also account for the patient's clinical condition. Once the patient starts to pass urine (at the partial anabolic stage?) the P will fall more rapidly than the urea, because the tubular reabsorption of P is still impaired (Platt 1950), while the inability to concentrate will prevent more than a few grams of urea being excreted, until the volume is very high and tubular function begins to return.

III C2. Changes in plasma cations.

Serum Ca was depressed to very low levels e.g., 2.5 meq./l., in the patients with very high P, but tetany was not observed because the acidosis, which was also present, would increase the proportion of ionised calcium by decreasing the base-binding capacity of protein. Albumin is generally low in these patients, although proteins were not actually estimated, so that the unionised Ca fraction must be very low.

In the cases where Mg was estimated, it was highest in/

in those with a high plasma K. As both these cations are present in higher concentrations in the tissues than in the E.C.F., one would expect both to increase in plasma if there is a rapid destruction of cellular material and incomplete removal of the products. The increase in plasma K is definitely toxic (Hoff et al. 1941), but Mg also has a narcotic effect (Schmidt & Greenberg 1935) and may be responsible in part for the comatose condition of these patients, (Hirschfelder 1934).

Blood cell K was frequently low as a result of the acidosis or hypotonicity or a combination of the two. The blood cell K is not necessarily an indication of the state of tissue K, but for a more detailed discussion of this question see Section VI.

III C3. Apparent hypotonicity.

There was considerable ionic hypotonicity during the anuric period as shown by the frequently low plasma Na, Cl and K_0 . Brown et al. (1955) found that plasma volume increased in anuric dogs, possibly due to endogenous production of water. However, due to the increase in urea and other organic compounds the total osmotic pressure may be higher than normal; e.g., in R.N., the sum of the decrease/

decrease in Na, Cl and bicarbonate=42 mOsmol./l., while the increase in urea alone = 46 mOsmol./l. This may be part of the explanation why one cannot raise the Na and Cl levels much in uraemia by giving saline without getting over-hydration. The plasma Cl particularly showed a marked improvement as soon as diuresis started and urea began to fall, although large amounts of Cl were being lost in the urine..

III C4. Treatment with steroids.

As few patients were treated with anabolic steroids and conditions were not always comparable, not many conclusions can be drawn. In the first case, stenediol seemed to delay the rise of urea, P, K and Mg although it had to be stopped later because of formation of intracellular oedema. In two cases where testosterone and Durabolin were given during the diuretic phase, there was a marked fall in urea and P, but this just continued the trend from the previous day. In two other instances when the steroids were given during the anuric phase there was only a slight temporary halt to the rise in K and urea, and these two died a few days later.

The value of these hormones lies more in their effect on tissue metabolism rather than renal function.

Although/

Although the kidney size was greater in animals treated with testosterone than controls (Freedman & Spencer 1957), Klopp et al. (1945) found little change in renal function tests so that the positive K and N balance must be a reflection of increased tissue anabolism. Masson, Corcoran & Page (1949) found that nephrectomised animals survived longer than controls, when treated with testosterone. The two patients that died had high plasma P as well as urea, so were probably actively catabolising and the steroids were not powerful enough to reverse this; in the other two, the anabolic phase had apparently started already, judging by the relative P and urea levels, so the steroids would potentiate this effect. In the patient treated with stenediol there was some fluctuation of P and urea, and the steroid possibly tipped the balance sufficiently to prevent the immediate rapid rise of metabolites.

These anabolic steroids probably have a useful part to play in the routine treatment of anuric patients, but if catabolism is rapid and generalised, they may do little more than arrest the rise of toxic products temporarily, but even this is a step in the right direction.

SECTION IV. BIOCHEMICAL TESTS IN THE DIAGNOSIS OF
HYPERPARATHYROIDISM IN PATIENTS WITH
RENAL CALCULI.

IV A. Introduction.

IV A1. General factors in stone formation.

Analysis of renal calculi reveals that the majority are composed of calcium, oxalate and phosphate, and occasionally magnesium, carbonate or urate; more rarely cystine stones occur but this is a result of an unusual tubular defect. Investigation of the underlying cause of stone formation must therefore take into account any factors which may influence the concentration and precipitability of these substances. Certain external factors such as infection, stasis, or presence of foreign particles, may play their part, but any further diagnosis rests mainly on demonstration of biochemical abnormality. Because of the relative frequency with which they occur in stones disorders of calcium and phosphorus metabolism are the obvious starting points for investigation. Their concentration in the urine may be increased if a diet rich in these elements is taken, along with large doses of Vitamin D or under other conditions promoting their absorption/

absorption. Apart from these dietary considerations, there are three main endogenous factors which affect calcium and phosphorus excretion: (a) hormonal activity, in particular the parathyroids, (b) bone metabolism, (c) acid-base balance.

IV A2. Renal calcification as a symptom of parathyroid tumours.

Several hormones have an effect on calcium metabolism, such as the thyroid and adrenalcortical hormones, but undoubtedly the main regulator of calcium and phosphorus metabolism is the parathyroid hormone. Originally connection was established between parathyroid tumours and the bone disease now known as osteitis fibrosa generalisata, (Mandl 1925), but in recent years it has become increasingly apparent that renal calculus formation, either with or without bone disease is also a significant feature. This was first pointed out by Albright, Aub & Bauer (1934). A list is given in Table IV 1 of the numbers of cases with bone and renal symptoms reported by various authors at different dates. All these are proven cases of hyperparathyroidism, although some were only discovered at autopsy; and as some of the references are/

TABLE IV 1. Occurrence of bone and renal symptoms in published cases of proven hyperparathyroidism.

Reference	Date	Total No. of patients	Bone Symptoms		Bone & Renal Symptoms		Renal Symptoms	
			No.	%	No.	%	No.	%
Norris	1947	314	191	61	101	33	17	5
Albright & Reifstein	1948	64	11	17	24	38	28	44
Lahey & Murphy	1953	29	16	55	9	31	4	14
Richardson	1953	11	-	-	7	64	4	36
Black, B.M.	1953	112	16	14	16	14	73	65
Hellström	1955	70	14	20	13	19	43	61
Pyrah & Raper	1955	32	13	41	14	44	5	16
	1955, 1934-53	19	9	-	10	-	-	-
	1953-55	13	4	-	4	-	5	-

TABLE IV 2. Incidence of parathyroid tumours in patients with renal calculi.

Reference	Date	Total No. Patients	No. with PTH. tumours	%
Griffin et al.	1938	1200	2	0.2
Barney & Mintz (Black's series)	1936	288	12	4
Keating & Cook (Albright's series)	1945		24	2
Beard & Goodyear	1950	150	12	8
Hellström	1955			
"	1940-49	1317	6	0.4
"	1950-54	766	22	3

are general reviews, a few of the cases may have been included more than once.

In the last paper nearly half the number had been recognised in the last two years, and it shows clearly what happens when systematic tests are made in patients with renal calculi.

IV A3. Parathyroid tumours as a common cause of renal calculus formation.

It is obvious from the above tables that nephrolithiasis is a very common manifestation of hyperparathyroidism, but the corollary that hyperparathyroidism is a common cause of renal calculi is not so well established, although there is evidence that it is present in a significant percentage of all calculus cases. Figures for the incidence of hyperparathyroidism in urinary lithiasis are given in Table IV 2. In the last reference there is again a striking increase latterly as a result of more complete routine investigations.

IV A4. Biochemical changes in hyperparathyroidism and factors affecting the tests.

These figures show that hyperparathyroidism has to be carefully considered in patients with renal calculi.

The/

The number of cases of hyperparathyroidism diagnosed in patients from the Urological Department of the Glasgow Royal Infirmary has been very small until recently, so it was proposed that more complete investigations of selected cases should be made.

There is still a good deal of argument as to the precise point at which the parathyroid hormone acts, but the symptoms of over-activity are well documented. The main biochemical findings are hypercalcaemia, hypophosphataemia and hypercalciuria; changes in phosphorus excretion are more difficult to identify since even in normal people there is a very considerable range. However, estimation of these quantities does not always give simple proof of hyperparathyroidism since they are influenced by subsidiary factors; for example the serum calcium may apparently be normal, but because of a decrease in serum proteins and thereby in bound calcium, the ionised calcium may in fact be high; or again, where the renal damage is considerable, retention of phosphate obscures the hypophosphataemia, and calcium cannot be excreted to the same extent. It was hoped that in the course of the work here more sensitive tests would be found/

found particularly for those cases where the changes are minimal.

These biochemical changes, while suggesting hyperparathyroidism, are sometimes, though not all, found in other conditions, which must also be considered in the diagnosis of the cause of calculus formation. Any disturbance of bone metabolism itself will profoundly affect the circulating and excreted calcium and phosphorus. For example both hypercalciuria and hypercalcaemia are found in myelomatosis, sarcoidosis, osteolytic metastases, or immobilisation, but in these instances differential diagnosis rests mainly on radiological evidence, which also distinguishes the osteitis fibrosa of hyperparathyroidism.

IV A5. Effect of acid-base balance on Calcium and phosphorus metabolism.

The third endogenous factor which can affect calcium and phosphorus metabolism is the acid-base balance which is intimately connected with renal function. An acid load causes an increase in phosphorus excretion since phosphate is the main buffering mechanism in the urine; this however is not such an important cause of stone formation since the urine is acid, which does not favour precipitation except/

except in the case of urate stones. On the other hand an excessive intake of alkalis along with a high Calcium diet may lead to stone formation because of the relative insolubility of calcium phosphate in an alkaline solution; magnesium stones are also formed at this pH. The milk-alkali syndrome as described by Burnett et al. (1949) exemplifies this; as a result of taking a milk diet and alkalis for treatment of ulcers, these patients develop a mild alkalosis and hypercalcaemia, and although the urine calcium may not be markedly increased, because of the alkaline pH it is easily precipitated. Improvement is brought about by modifying the diet. In these instances the kidney is merely showing its capabilities in dealing with abnormal loads, although eventually it may become permanently impaired. There is another group however in which the primary lesion is with the kidney itself. In "renal tubular acidosis" the tubules are apparently unable to excrete hydrogen ions; as a result fixed cations are lost, particularly when an acid load is given. Calcium is one of the fixed cations lost, and as the urine tends to be alkaline, conditions are encouraging for stone formation, particularly as the ability to concentrate may still/

still be present. Albright & Reifenstein (1948) describe three such cases who showed improvement when treated with alkalis, and although the urine remained alkaline, the hypercalciuria decreased, since in the presence of adequate amounts of base the calcium stores were not required. The aetiology of this disease is still obscure but in some cases previous infection may damage the tubules to produce an analogous type of impaired function. Renal rickets, or in adults some forms of osteomalacia, are similar conditions, but glomerular function is also impaired, and the hypercalciuria proceeds to the extent that bone formation is inadequate.

The Fanconi syndrome, reviewed by McCune, Mason & Clarke (1943) is another form of tubular defect in which there is an increased excretion of organic acids; although the buffering mechanism is still functioning to a certain extent, the excess anions still require extra cations, which again means a hypercalciuria.

All these various factors have to be borne in mind when making investigations in patients with renal calcification. The tests and their results in these different/

different conditions are summarised in Table IV 3. As in the past sufficient evidence may not have been obtained in these cases, more intensive studies were to be the purpose of this investigation.

TABLE IV 3. Tests in diseases involving Ca and P metabolism.

Disease	Serum			Urine			Remarks
	Ca	Alk. P ^{ase}	HCO ₃ Cl	Ca	P	PH	
1. Hyperparathyroidism	+	-	0+	+	+	+	
2. Xs. Vit. D.	+	-		+	+	+	
3. Sarcoidosis.	+	0	+	+			Differentiate radiologically.
4. Bone metastases	+	0+	0+	+			
5. Paget's disease	0+		++	+			Proteins abnormal.
6. Myelomatosis.	+	-0	0	+			
7. Immobilisation	0+	0	0	+		+	
8. Idiopathic hypercalcaemia	-0	-	+	+		0	
9. Renal tubular acidosis.	-0	-	0+	+	0+	+	(Urine NH ₄ & T.A. decreased.)
10. Milk-alkali syndrome	+	0	0	+	0	+	(Glycosuria. (Aminoaciduria. (Urine NH ₄ & T.A. increased.)
11. Fanconi.	-0	-	+	-	0	+	
12. Osteomalacia. Rickets.	-0	-0	+	-	-	-	
13. Hypoparathyroidism	-	+	-0	-	-	-	
	+ Increased	0	Normal	-	Decreased		

SECTION IV. BIOCHEMICAL TESTS IN THE DIAGNOSIS OF
HYPERPARATHYROIDISM IN PATIENTS WITH
RENAL CALCULI.

IV B. Results.

IV B1. General procedure.

During the period January 1955 - September 1957, blood analyses and other tests have been carried out in 60 patients with renal calculi. These patients were to some degree selected from the total number, being for the most part those with bilateral or recurring stones or calcinosis. Initially the usual procedure was followed of obtaining one blood specimen from each patient for the estimation of serum calcium, inorganic phosphorus and alkaline phosphatase. However, when it was realised that the blood levels were subject to some fluctuation and that any abnormal changes were likely to be minimal, it was found advisable to repeat the blood estimations at least once, and in addition the 24 hour urinary calcium excretion was also found to be a useful test. It was also found necessary to modify the normal limits beyond which suspicion of biochemical abnormality could be entertained. The usual range for serum/

serum Ca is taken as 4.5 - 5.5 meq./l., and for inorganic P 2.0 - 4.0 mg./100 ml., but for the present purpose serum Ca exceeding 5.25 meq./l., or P less than 2.5 mg./100 ml. particularly if they were consistently at these levels, while not being considered abnormal when taken in conjunction with other findings could support the diagnosis.

IV B2. Results of single blood estimations.

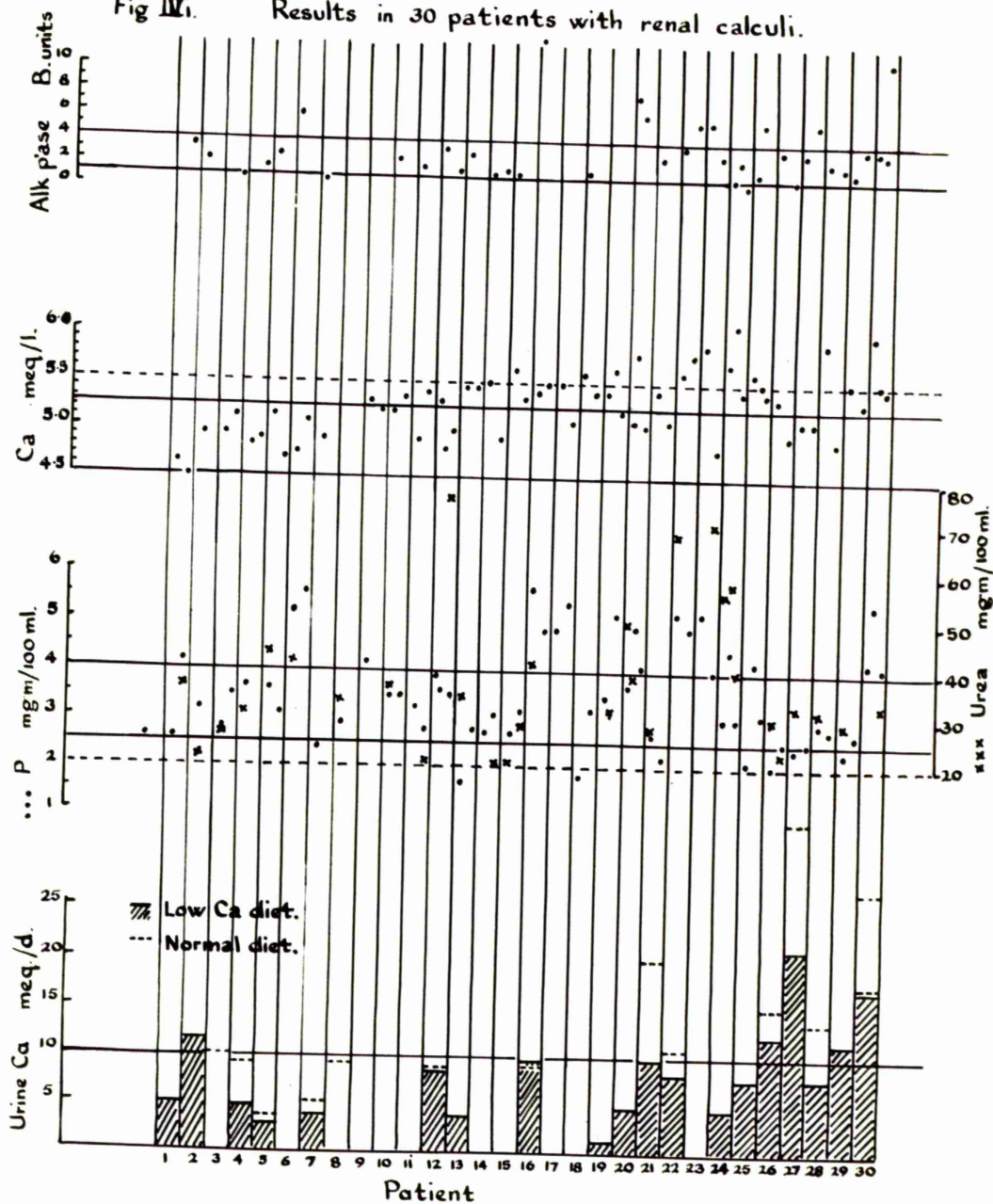
In 1955 14 single blood tests were done, of which only four were wholly normal as judged by these limits. 8 had a serum Ca above 5.3 meq./l., only one of whom had a lowered P as well, while two others had a lowered P but normal Ca. In this group the highest level of Ca was 5.8 meq./l., and the lowest P was 1.7 mg./100 ml. (though not in the same patient), so that at the time these were not considered sufficiently abnormal to warrant further study. However, when these tests were repeated in seven others with somewhat similar results within a few days, only one was found to be within its original limits, and it was decided that in future a more thorough investigation would be carried out. In the remaining period 16 further single estimations were done, but all but two of these were completely normal.

IV B3./

IV B3. Results of repeated blood estimations.

In 30 patients the results were as shown in Figure IV 1. Over half gave results which fluctuated within and without the normal range. Most of those with a lowered serum P were also associated with Ca over 5.25 meq./l., but as the low P was a relatively less common finding than a raised Ca, it follows that P was normal in many of those with a raised Ca. However, P estimation is not a good guide in patients with renal involvement, since it tends to be retained along with nitrogenous products if the kidney function is at all impaired. For this reason the blood urea should always be done at the same time to give an indication of this, and has been plotted on the chart with the P. For example, six of these patients (Nos. 6, 16, 20, 22, 23 and 24) had P slightly above normal and urea greater than 40 mg./100 ml., while another two (Nos. 5 and 12) had raised urea, but normal P, which would perhaps have been subnormal otherwise. Plasma proteins were also estimated in most cases, as a low protein value by decreasing the bound Ca may mask an increase in the ionised Ca, which is the fraction in which we are interested. Only one had/

Fig IV. Results in 30 patients with renal calculi.



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had a protein level below 7.0 g./100 ml. (No. 14, 6.8 g./100 ml.) although in the majority there was a high globulin fraction and lowered albumin.

IV B4. Plasma alkaline phosphatase results.

Alkaline phosphatase is not generally helpful in the diagnosis of hyperparathyroidism unless the bone metabolism is involved and osteoblastic activity is increased (Keating and Cook 1945). These patients were all presenting with renal symptoms and none had any obvious bone changes, although special radiological examination of the skeleton was not generally made. Three however, did have an elevated alkaline phosphatase and two others on one occasion (22,23). Three other patients (25,27 and 30) who had a normal phosphatase when first examined, had high values after a few days on the standard low Ca diet, 2 having a very high urinary Ca excretion. It appeared then that their diet was sufficiently good under normal circumstances so that in spite of a high urinary loss, heavy demands on the bone minerals were not necessary except when intake was restricted.

IV B5. Urine calcium excretion under standard conditions.

In view of the equivocal results obtained from repeated/

repeated blood estimations, other tests of abnormal parathyroid function were sought. Hypercalciuria being a significant occurrence in this disease, Ca excretion in 24 hour urine collections was estimated under standard conditions. On a low Ca diet of 8 meq. Ca/day after 3 days for equilibration, the normal person should not excrete more than 5 - 8 meq. Ca/day in the urine (Black, B.M. 1953, Albright and Reifenstein 1948). Over 10 meq./day is definitely abnormal. At first, if the serum analyses gave one or more suspicious results, the patient was put on the standard low Ca diet for 6 days, the urine being collected over the last 3 days of this period. Latterly an initial 24 hour collection was made while the patient was still on the normal unstandardised diet, as it was found that if Ca excretion on this diet were less than 10 meq. it was unlikely that more would be excreted when on a low Ca diet. This saved time, since the patient generally required operation without delay, so that opportunities for the 6 day balance were not always available.

21 of the 30 patients had urinary Ca estimated in this way, and in 7 (Nos. 2, 16, 21, 26, 27, 29 and 30) it was/

was 10 meq./day or more and over 8 meq./day in two others (12 and 21). Only one of these 7 had completely normal blood results, so that support was given to the rather equivocal figures. This test also has its limitations as urine calcium may be low if renal function is very poor (e.g. Nos. 5, 22 and 24).

The hypercalciuria did not necessarily depend on a raised serum Ca. In only one case (No. 30) with hypercalciuria was the serum Ca above 5.5 meq./l., and in the patient with the highest Ca excretion of the series, it was normal.

IV B6. Equivocal results in 8 patients.

Of the 60 patients with renal calculi in whom some or all of these tests were done, 8 emerged as possible candidates for exploration of the parathyroids, taking as minimal criteria at least three abnormal results from repeated estimations of serum Ca, P and urine Ca. Even so, the limits are somewhat arbitrary and some of the results are so very much on the borderline, allowing for experimental error, that one hesitates to recommend surgical intervention. To illustrate this, the results from these 8 patients are given in full (Table IV 4).

IV B7/

TABLE IV 4. Results in eight patients with renal calculi.

<u>Patient</u>	<u>Serum Ca</u> <u>meq./l.</u>	<u>Serum P</u> <u>mg./10⁰ ml.</u>	<u>B.U.</u> <u>ml.</u>	<u>Urine Ca</u> <u>meq./day</u>	<u>Remarks</u>
21.J.W.	* 5.4	2.7	28	* 10.0	
	5.1	* 2.2			
22.A.L.	* 5.6	5.2	* 68	* 8.2	
	* 5.8	4.9			
16.S.N.	* 5.4	5.7	* 42	* 9.7	High alk.p'ase.
	* 5.5	4.9			
27.J.S.	5.1	* 2.4	33	* 21.4	Alk. p'ase rose
	5.1	* 2.5			on low Ca diet.
26.A.H.	* 5.4	* 2.0	30	* 12.1	
	5.0	* 2.5			
29.M.D.	* 5.5	* 2.3	29	* 11.5	
	* 5.3	2.7			
25.J.McI.	* 5.6	* 2.1		7.6	Alk. p'ase rose
	* 5.5	4.2			on low Ca diet.
	* 5.5	4.2			
30.P.McM.	* 6.0	4.2			
	* 5.4	4.5		* 17.3	Alk. p'ase rose
	* 5.4	4.1	33		on low Ca diet.

* Abnormal or equivocal results.

IV B7. Acid-base balance.

In the differential diagnosis, acid-base balance is important since renal tubular acidosis may cause hypercalciuria, although the serum Ca is normal or low. The most convenient way of checking this is by estimating the plasma chloride and bicarbonate, since the Cl is generally elevated to compensate for the lowered bicarbonate. This was done in half the total number of patients, one (M.B.) of whom was found to have quite a marked acidosis and a high chloride.

	Serum Ca	Plasma Cl	HCO_3^-	Serum P	B.U.
	meq./l.			mg./100 ml.	
M.B.	4.7	113	16	2.6	37
	4.5	112	19	4.4	60

According to Albright & Reifensstein (1948), there is a primary failure to excrete acid, so that instead of eliminating hydrogen ions other cations are lost, including Ca, and this in conjunction with the alkalinity of the urine favours precipitation. In this particular patient, although the urine was neutral or alkaline, there was no evidence of an increased Ca excretion, being 5 meq./day on the low Ca diet.

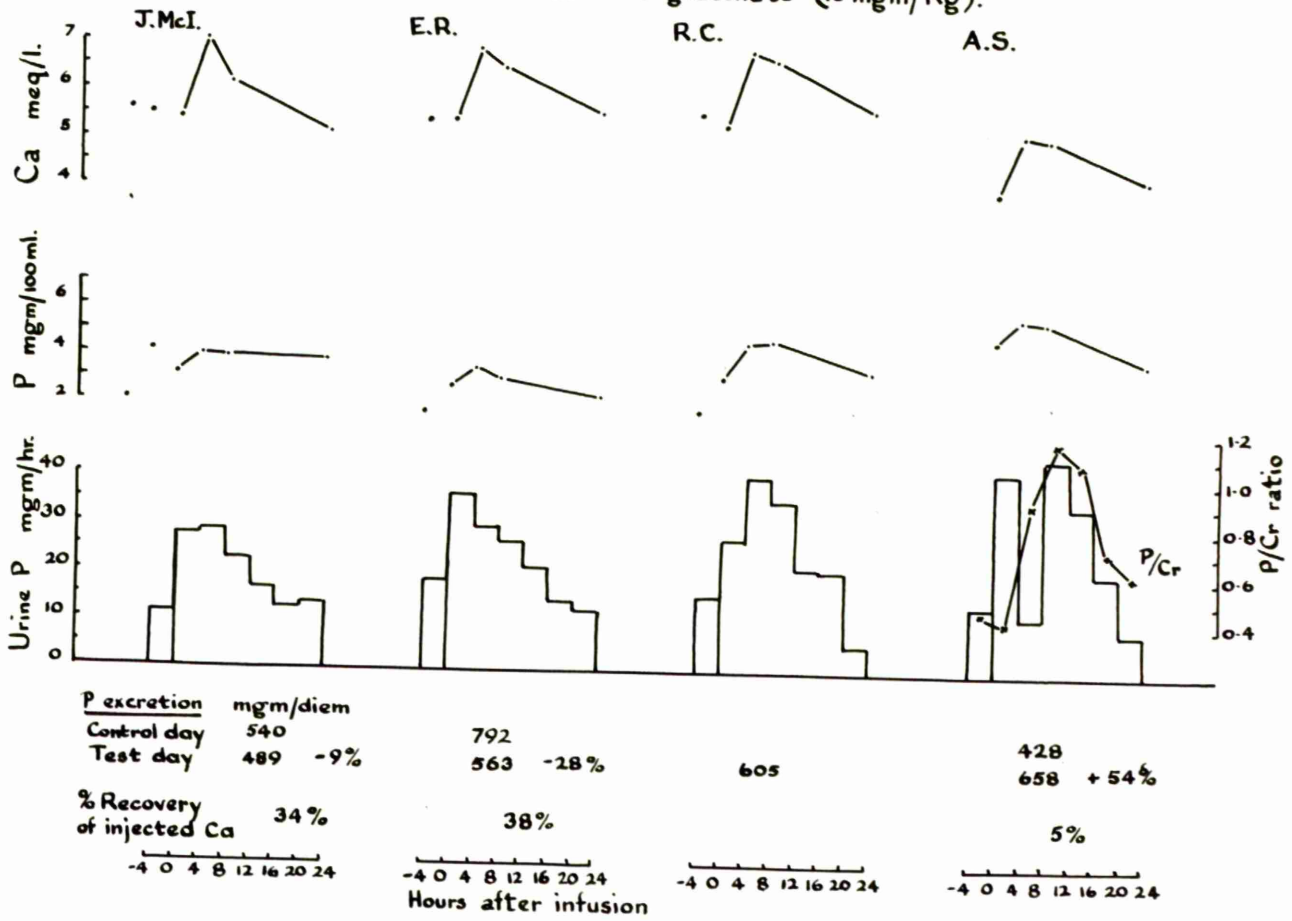
IV B8/

IV B8. Calcium infusion test.

In the search for a suitable test of parathyroid activity the calcium infusion test has been advocated by Howard, Hopkins & Connor (1953) and Nordin & Fraser (1954). The two vary in the criteria taken; Howard assesses the decrease in P excretion in the 24 hour period compared with a control day, while Nordin follows it in 2 - 4 hour periods for the 24 hours of the test. The latter was the procedure carried out here although in 3 cases it was also compared with the 24 hour excretion. Four such tests were carried out, three in patients with renal calculi and blood results which suggested a degree of parathyroid hyper-activity, and the fourth in a patient with idiopathic hypoparathyroidism by way of a contrast. 15 mg. Ca (as gluconate in saline) /Kg body weight was infused over a period of 4 hours; blood was taken at 0, 4, 8, 24 hours and urine collected at 4 hourly intervals. The results are shown in figure IV 2.

It will be seen that the serum Ca rose by approximately 1 - 5 meq./l. in the three patients following the 4 hour infusion, returning more or less to normal after/

Fig. 12. Results after IV. infusion of Calcium gluconate (15 mgm/Kg).



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after 24 hours. In A.S. the hypoparathyroid patient, it did not rise quite so much, and had not returned to its original level after 24 hours. Plasma P rose in all, 0.8 - 1.4 mg./100ml., but the response was variable so that there were no clear-cut differences. Howard et al. found that plasma P rose up to 2 mg./100ml. by 4 hours, falling to normal in 24 hours in normals, but there was not so much change in either hypo- or hyperparathyroidism. Nordin & Fraser also found the plasma P to be raised in all cases, although least in the group with osteomalacia, who were presumed to have secondary hyperparathyroidism. Two surgical hypoparathyroid cases had a similar rise but it remained high, in contrast to A.S.

It is not the blood results however which are taken as diagnostic criteria but the urinary excretion of Phosphorus. The hypothesis is that the I.V. calcium depresses parathyroid hormone production and so simulates a hypoparathyroid state with decreased P excretion, while those with a parathyroid tumour, not being under normal physiological control, will be affected to a lesser extent. In Howard's normals, 24 hour urine phosphorus was approximately 20% less on the day of infusion than the previous/

previous control day, was increased or decreased only slightly in the hyperparathyroids, but rose 100% in the hypoparathyroids. A.S. showed the biggest increase by 54%, J. McI. was -9% and E.R. -28%. When the 24 hours of the day of infusion were split into 4 hour periods, there was a marked increase in the rate of P excretion up to 12 hours following the start of infusion; the P diuresis was particularly marked in the case of A.S., although the urine volume in the second period was so small that P/hr. was less, although the P concentration was very high. In E.R. and R.C., the rate of excretion of P in the last 4 hour period was less than the comparable period before starting the infusion, while J. McI. was much the same. These results are in direct contrast to Nordin's, who found a decrease in the rate of excretion in the osteomalacia group from infusion time onwards, and in the normals from 8 - 16 hours. He found a more constant fall in the P/Creatinine clearance ratios, but because of the non-specificity of the creatinine estimation in blood, this was not done; in any case, where the plasma levels are known to be changing as they are in these cases, clearance ratios cannot be calculated with much degree of accuracy. The ratio/

ratio of urinary excretion of P and Cr was calculated for A.S., and it showed a large increase from 4 hours onwards. It is interesting to note that in spite of the large variations in urinary volumes in the first 12 hours being 920, 60, 140 ml. for the 4, 8, 12 hour periods respectively, the P/Cr ratio did not rise until the second period, suggesting that the exaggerated increase in P excretion rate in the first 4 hour period was due to the marked diuresis, and increased glomerular filtration rate.

The calcium infusion test was not continued as from these results there did not appear to be a sufficiently striking difference between normals and people with a minimal disturbance in parathyroid function such as we had here.

IV B9. Urine Phosphorus - Creatinine ratios.

It has been suggested that urine P/Cr ratios might be worth investigating since in hyperparathyroidism one would expect an increased P excretion (or decreased P reabsorption) in comparison with the constant creatinine excretion. This was therefore tried in 7 patients who were on normal diets as well as 7 who were on the low calcium diet. It was found there was a considerable variation/

variation from day to day when it was estimated in the 24 hour collections, but also when two or more periods of 1 - 4 hours were taken at different times of the day (See Table IV 5). Thus A.C. had three consecutive P/Cr ratios for 24 hour periods of 0.83, 0.46 and 0.36 while for two 1 hour periods they were 0.66 and 0.55. Similarly in J.S. for the 24 hour period, P/Cr values ranged from 0.40 - 0.58 and when one of these days was partitioned into 4 hour periods the values obtained ranged from 0.33 in the early morning to 0.72 in the evening. A.S., the hypoparathyroid patient had results which were of the same order, although one would have expected them to be much lower; the 24 hour period ratio was 0.69, while for two shorter periods in the early morning it was 0.41 and 0.94, but in the latter example the patient was under treatment, which may account for the divergence. When she was given parathyroid hormone in the Ellsworth-Howard test, the ratio did increase abruptly to the very high level of 2.12, showing that the underlying assumption was correct.

From these few examples, variations from day to day appeared to be greater than variations in the hypo- and hyperparathyroid/

TABLE IV 5. Urine phosphorus/creatinine ratios.

Patient	Plasma P mg./100 ml.	24 hr. spec. (Normal diet)	24 hr. spec. (Low Ca diet)	Shorter periods time
20.A.C.	4.2		0.83 0.46 0.36	0.66 10-1100 hrs. 0.55 11-1200 hrs.
27.J.S.	2.4	0.48 0.40	0.45 0.46 0.58	0.33 07-0900 hrs. 0.43 09-1100 hrs. 0.72 11-1500 hrs. 0.72 15-1900 hrs. 0.60 19-2300 hrs. 0.51 23-0700 hrs.
12.R.M.	3.7	0.42 0.56	0.45 0.43 0.38	
7.I.B.	2.4	0.70 0.61	0.40 0.36 0.60	
21.J.W.	2.4	0.75	0.59 0.40 0.52	
M.G.		0.65 0.54	0.52 0.50 0.59	
3.J.H.	3.1	0.66		
M.W.		0.60		
A.S.	4.9	0.69		0.45 05-0900 hrs. 0.94 07-0900 hrs.
			I.V. P.T.H.	2.12 09-1100 hrs. 1.60 11-1300 hrs.

hyperparathyroid states, and certainly it would be impossible to pick out the borderline cases with minimal changes since the range is so varied.

ADDENDUM.

Since this work was completed, parathyroid adenomas have been removed from 5 patients investigated by the Biochemistry Department of the Glasgow Royal Infirmary. The results of the various investigations are given in Table IV 6, for comparison with the results given above. One of these patients (M.C.) had renal calculi with no obvious bone changes, one (M.S.) had bone decalcification and no renal damage, and in the other three, both symptoms were present. In all except one case, the results were fairly conclusive. In B.F. the changes were minimal, but because of the convincing history and the hypercalciuria, she was admitted for operation, and a parathyroid adenoma was found. The most consistent finding in all the patients was the hypercalciuria, which fell abruptly to normal following removal of the tumour (e.g., M.L.). The various points mentioned above applied in these cases too; for example, the variability of the results from day to day, the necessity for renal function tests, the raised phosphatase levels when bone changes are involved, and hypercalciuria not necessarily dependent on hypercalcaemia.

TABLE IV 6. Plasma and urine results in 5 patients with proven hyperparathyroidism.

Patient	Date	Ca mg./l.	P mg./100 ml.	B.J. ml.	Alk. Phos K.A. Units	Urine Ca		Remarks
						meq./d.	Normal Low Ca diet diet	
M.C.	20/4	5.8	2.2	41	10	15		M. 35 years Recurrent calculi Urea clearance 63% PTX 3/5.
	24/4	6.7	1.7	49	11	23		
	1/5	6.8	2.0		13	19		
B.F.	31/5	4.6	3.3	31	11	7		F. 48 years Recurrent calculi Peptic ulcer. 2 fractures. Ur. Clearance 86% PTX 24/4
	21/3	5.5	2.5		7	21	14	
	4/4 9/4	5.2 4.8	3.1 2.6	27 28	7 7	23 24	19	
M.L.	1/5	4.9	2.9	25	8	20		F. 48 years Bilat. calculi. Bone changes PTX 26/10
	12/9	6.3	2.5		42	34		
	23/9	6.0	2.0		40	32		
	20/10	5.3	2.5	28	48	43		
	28/10	4.1	2.8	46	43	6		

* Alkaline phosphatase in King Armstrong Units (normal range 4-14 units) not Bodensky units as previously.

Table IV 6. (Contd.)

Patient	Date	Ca mg./l.	P mg./100 ml.	B.U. ml.	Alk. p'ase K.A. Units	Urine Ca		Remarks
						Normal diet	Low Ca diet	
M.A.	9/5	6.4	1.4		90	12	14	F. 34 years Calcinosis. Bone changes. Urea clearance 47% PTX 12/6
	17/5	5.7	1.0	20	91	19	12	
	23/5	5.2	1.3		74	20	9	
	19/6	3.6	2.2		77		8	
H.S.	28/9	5.8	3.7	22	24	19		F. 51 years Bone decalcification PTX 8/10
	1/10	6.3	2.2		30	18		
	14/11	4.6	2.3	23	44			

PTX - Parathyroid adenoma removed.

SECTION IV. BIOCHEMICAL TESTS IN THE DIAGNOSIS OF
HYPERPARATHYROIDISM IN PATIENTS WITH
RENAL CALCIFICATION.

IV C. Discussion.

IV C1. Difficulties of diagnosis.

This is too small a series from which to draw many conclusions except to emphasise again the difficulties in diagnosing hyperparathyroidism in cases where the kidneys are involved. Renal failure leads to conditions resembling hypofunction of the parathyroid (high serum P, low Ca), which may mask a primary hyperfunction, or alternatively leads to a secondary hyperplasia of the glands. (Albright & Reifenshtein 1948). This makes interpretation of the results very difficult, particularly with regard to phosphorus levels. In addition, results may vary considerably from day to day or at longer intervals, so that it is essential to repeat the determinations of serum Ca and P at least once. Thus nearly half the patients here had a normal and high serum Ca (more than 5.3 meq./l.) on different occasions. Keating & Cook (1945) found this too in a quarter of their series. Serum Ca levels of 5.3 meq./l./

5.3 meq./l. are not too low to be considered seriously in the diagnosis; 16% of Keating's cases (1945) and 7% of the Mayo Clinic series (Black, B.M. 1953) with proven parathyroid tumours had serum Ca between 5.3 and 5.5 meq./l., while in nearly half the latter series it was less than 6 meq./l. Small deviations from the normal are therefore not uncommon. Beard & Goodyear (1950) even report one patient from whom a tumour was removed with a serum Ca not greater than 5.3 meq./l., P not less than 2.8 mg./100 ml., and urine Ca 6.5 meq./day.

IV C2. Significance of hypercalciuria.

Tests based on hypercalciuria are more significant, although again it must be remembered that in the presence of more severe renal damage this too will be diminished. It is generally accepted that after 3 days on a low Ca diet (preferably 6 days) the urine Ca should not exceed 8 meq./day, and certainly not over 10 meq./day, (Albright & Reifenshtein 1948, Black, B.M. 1953, Pyrah & Raper 1955), and even although other findings do not necessarily support a diagnosis of hyperparathyroidism, the very presence of a high Ca concentration in the urine is a significant factor in stone formation, although the primary cause may still be obscure/

obscure. Here 7 out of 20 cases had a definite hypercalciuria. Flocks (1940) found a large proportion (66%) of calculi patients had "idiopathic hypercalciuria", without other definite signs of hyperparathyroidism, although he does not give many figures to illustrate this. Of course other causes of hypercalciuria must be differentiated (see Table IV 3); the one with which it is most likely to be confused is renal tubular acidosis, and for this reason plasma bicarbonate should always be estimated at least once during the investigations. Also Ca excretion does depend to a certain extent on body size; Knapp (1947) found that urinary Ca/Kg body weight was constant at all ages over 20 years for a constant intake/Kg.

IV C3. Minimal criteria.

It is suggested that from any patient requiring investigations of parathyroid function, at least two blood specimens should be obtained for Ca and P estimations, and one 24 hour urine collection on a normal diet for estimation of Ca excretion; if the latter is over 10 meq./day, then a further 24 hour collection should be made after 3 days on a low Ca diet. If more than two of these five estimations are abnormal or equivocal, i.e., Serum Ca over 5.3 meq./l./

5.3 meq./l., P less than 2.5 mg./100 ml., and urine Ca over 8 meq./day on a low Ca diet, then further tests must be done and the question of parathyroid tumour discussed. In addition blood urea should be estimated at the same time as a rough index of renal function, plasma chloride and bicarbonate to exclude tubular defects, and plasma proteins as a guide to non-ionised Ca and to exclude myeloma. If the bones are involved radiological examinations will give further differential evidence. Alkaline phosphatase may or may not be increased in hyperparathyroidism, depending on the degree of balance and severity of the disease; for example, two patients with gross hypercalciuria and no obvious bone lesions, had a raised alkaline phosphatase only when the calcium intake was restricted, and if this diet had been continued long enough would undoubtedly have resulted in bone dissolution. It is also important that these tests should be repeated at intervals of months or even years, as the serum abnormalities may only appear some considerable time after development of renal symptoms.

IV C4. Calcium infusion test.

Intravenous calcium gluconate was infused in 3 patients/

patients with renal calcification and 1 with idiopathic hypoparathyroidism, but the results obtained were not sufficiently clear-cut to warrant its inclusion as a routine test. Howard's (1953) criterion of change in 24 hour P excretion seems possibly more distinctive than Nordin's (1954) P/Cr clearance ratios, which are open to some objections, the main one being the value of such ratios when the blood levels are altering, as they are here. The pattern of P excretion was roughly the same in all 4 patients, including the hypoparathyroid one, but when compared with the previous 24 hour excretion, there was a marked increase in the hypoparathyroid patient but a decrease (8% and 28%) in the other two. Baylor et al. (1950) found a decrease of 7 - 20% in 3 patients after a slightly different Ca infusion. None of these patients showed a decrease in P excretion in the 4 hourly periods following infusion, such as Nordin & Fraser (1954) found in their osteomalacia group with presumed secondary hyperparathyroidism or Justin-Besançon et al. (1954). The increase in plasma P was also very similar in all four patients, so this was no help in distinguishing between the conditions.

The/

The basis of this test is not entirely explained. According to Nordin and Howard, the high serum Ca suppresses parathyroid action, except in those with tumours who are no longer under normal physiological control. In other words, normal people should react as a hypoparathyroid, with an increased P reabsorption, but while there was a decreased P excretion in the normals, there was a marked increase in the hypoparathyroid patient. On the other hand Schaaf & Kyle (1954) and Thompson & Hiatt (1955) found no change in % P reabsorbed or TMP (maximum tubular reabsorption of P) when Ca was infused. Part of the change in P excretion may be due to increased glomerular filtration rate, such as was seen in the first period in A.S., where the P/Cr ratio was little changed although P output trebled, but after that there was an undoubted rise in P secretion (or decreased reabsorption). The increase in plasma P in all cases is also not very satisfactorily explained; it was not correlated with P retention since it was highest 4 hours after the start of the infusion during which time there was a marked increase in P excretion.

IV C5. Urinary Phosphorus/Creatinine Ratios.

The final test investigated here was the ratio of phosphorus/

phosphorus to creatinine in the urine, as suggested by Nordin (1955). This was found to be of little value as day to day and hourly variations were greater than changes in parathyroid activity. Some have advocated it using random specimens but this is even more unreliable as the results in U.S. demonstrate, which is not surprising considering the diurnal variation of P excretion (Olleyos & Winkler, 1943). In addition, % P reabsorption as it is sometimes expressed $(= \frac{\text{Filtered P} - \text{excreted P}}{\text{Filtered P}})$ is decreased in chronic renal insufficiency (Schaaf & Kyle 1954), and in primary renal tubular acidosis (Scheiss et al. 1948), although Pitts & Alexander (1944), found no change in TMP in acidosis in dogs; both these conditions may occur in the patients we are investigating. McGeown (1957) found that to obtain any significance the P/Cr ratios had to be related to the plasma P, but she agrees it is no help in the borderline cases.

None of these tests is sufficiently sensitive for definite diagnosis of parathyroid tumours in patients with some degree of renal impairment and minimal changes in the blood. The best alternatives are estimations of serum Ca, P, urea and bicarbonate and urine Ca repeated at fairly frequent/

frequent intervals in patients in whom the condition is suspected, so that consistent results indicative of the progress of the disease may eventually warrant surgical exploration of the parathyroid glands.

SECTION V. MAGNESIUM METABOLISM IN VARIOUS ELECTROLYTE
DISTURBANCES.

V A. Introduction.

V A1. General.

In recent years a considerable amount of work has been done on the various cations and anions of the body fluids, but in spite of large numbers of papers on sodium, potassium, calcium, chloride, bicarbonate and phosphate, magnesium has been largely neglected. There have been general reviews (Schmidt & Greenberg 1935, Haury 1942, Lancet annotation 1954, and Elkinton 1957) and several papers mention raised or lowered levels in various diseases, but as to its metabolism, we know little more now than 10 - 20 years ago. Since the isolation of many enzyme systems, we do however know that it plays a part in the activation of several of these, for example, the phosphatase, enolase and carboxylase enzymes (Lehninger 1950), while the breakdown of A.F.P. is inhibited (Greville & Lehman 1943) and the A.T.P. concentration in muscle is increased by its influence (Flink et al. 1954).

V A2. Serum magnesium in renal disease.

As far as urological patients are concerned, it has been/

been known for a long time that in renal failure high values for serum magnesium are often obtained, (Watchorn & McCance 1932, Hirschfelder 1934, Brookfield 1937, Haury & Canterow 1942), although the earlier papers of Denis & Hobson (1923), Rabinowitch (1925) reported little alteration. In hypertensive patients with renal disease it is also increased more frequently than in hypertensive patients with normal renal function (Walker & Walker 1936, Haury & Canterow 1942). Hirschfelder (1934) pointed out the danger of giving Epsom salts as a purgative or I.V. magnesium salts to nephritic patients as this could lead to very high magnesium levels eventuating in coma. On the other hand, low magnesium levels were sometimes found in patients with chronic glomerulonephritis, in which case administration of magnesium salts improved the twitchings and muscular irritability (Hirschfelder (1934).

V A3. The effect of magnesium on nerve and muscle irritability.

These neurologic and muscular manifestations have been shown to occur in rats on a magnesium free diet, who developed spasticity, cardiac arrhythmia, vasodilatation and tetany (Kruse, Orent & McCollum 1932), while cattle and/

and sheep may develop a disease known as grass staggers, which has been shown to be due to magnesium deficiency (Sjollem 1932). Cardiac arrhythmia from digitalis can be depressed by administration of magnesium (Szekely & Wynne 1951). Magnesium has also been implicated in epileptic attacks, low values having been found in serum and blood (Hirschfelder & Haury 1935; Blumgarten & Rohdenburg 1927), although this has not always been substantiated (Greenberg & Aird 1938).

V A4. The effect of hormones on magnesium metabolism.

Parathyroid hormone was one of the first hormones to be prepared, so its effect on magnesium was investigated in several early papers. Injection of the hormone led to a slight decrease in serum magnesium (Watchorn & McCance 1932, Cantarow, Haury & Whitbeck 1938) and an increased urinary excretion (Bulger & Gausmann 1933), with similar changes in hyperparathyroidism (Tibbetts & Aub 1937), although Greenwald & Gross (1925) found it was more variable. On the other hand Hirschfelder (1934) and Bulger & Gausmann (1933) both describe a low serum magnesium in hypoparathyroidism.

Magnesium and calcium infusions had a depressive effect/

effect on the serum calcium and magnesium respectively (Schmidt & Greenberg 1935, Brookfield 1934, Haury & Cantarow 1940) while the coma induced with high serum magnesium levels could be alleviated by calcium (Hirschfelder 1934). Intravenous magnesium also increased the urinary loss of calcium and vice versa (Schmidt & Greenberg 1935, Tibbetts & Aub 1937, Womersley 1956).

Other hormones have varying effects, again not very well marked. In hyperthyroidism the serum magnesium is normal but according to Soffer et al. (1941) the ultrafilterable fraction is decreased, while in myxoedematous or thyroidectomised patients the ionised magnesium is increased. This gives a neat correlation between the levels of free magnesium and muscular irritability in these conditions, but while this work has been confirmed by Dine & Lavietes (1942), other authors could find no such variations (Cope & Wolff 1942, Bissell 1945). In diabetic coma, serum magnesium levels are frequently above normal, although the body may actually be deficient (Atchley et al 1933, Martin & Wertmann 1947, Nabarro, Spencer & Stowers 1952). According to Schmidt & Greenberg (1935) administration of magnesium salts may produce hyperglycaemia.

Serum magnesium has been reported as being normal in/

in both Addison's and Cushing's diseases (Tibbetts & Aub 1937a), although Hills et al. (1955) have found that serum magnesium was increased in adrenal insufficiency when salt was withdrawn, and Conway & Hingerty (1946) found that muscle magnesium was increased as well as in serum after adrenalectomy in rats. On the other hand Hills et al. (1955) and Haynes, Crawford & De Bakey (1952) also suggest that there is magnesium retention after giving ACTH with a rising serum magnesium and decreased urine magnesium. This was also observed in patients post-operatively (Haynes et. al. 1952), but elsewhere low levels of serum magnesium have been reported post-operatively (Martin et. al. 1950, Flink et al., 1954 Levey et al. 1956), although in these cases it was mostly due to heavy losses and inadequate replacement. Haynes et al. (1952) also suggested that the urine magnesium was reciprocal to the urine potassium, although this has not been substantiated (Hills et al. 1955). There have however been other suggestions of magnesium/potassium antagonism in the serum, for example, Hirschfelder's (1935) observations in epileptics, and magnesium paralysis being relieved by potassium (Smith 1941), while intravenous magnesium depressed serum potassium (Smith 1949) and urine potassium (Womersley 1956). But again this is not a constant/

constant finding, and magnesium and potassium rise and fall in parallel, for example in diabetic coma and uraemia.

It can be seen from this brief survey that much remains to be clarified before we can understand the role of magnesium in the body. While it is possible to perceive some sort of pattern, it is built up from very slender threads of evidence; with all the various methods of magnesium estimation, different ranges of normal values, variations so slight but taken as significant, and other factors accepted uncritically, it is hardly surprising there are so many conflicting or unsubstantiated theories. More information on the subject was therefore sought by carrying out magnesium estimations on some of the patients discussed in the previous sections, as they offered a fair range of conditions and electrolyte disturbances.

SECTION V. MAGNESIUM METABOLISM IN VARIOUS ELECTROLYTE
DISTURBANCES.

V B. Results.

V B1. Serum magnesium, calcium, and phosphorus in patients
with renal calculi.

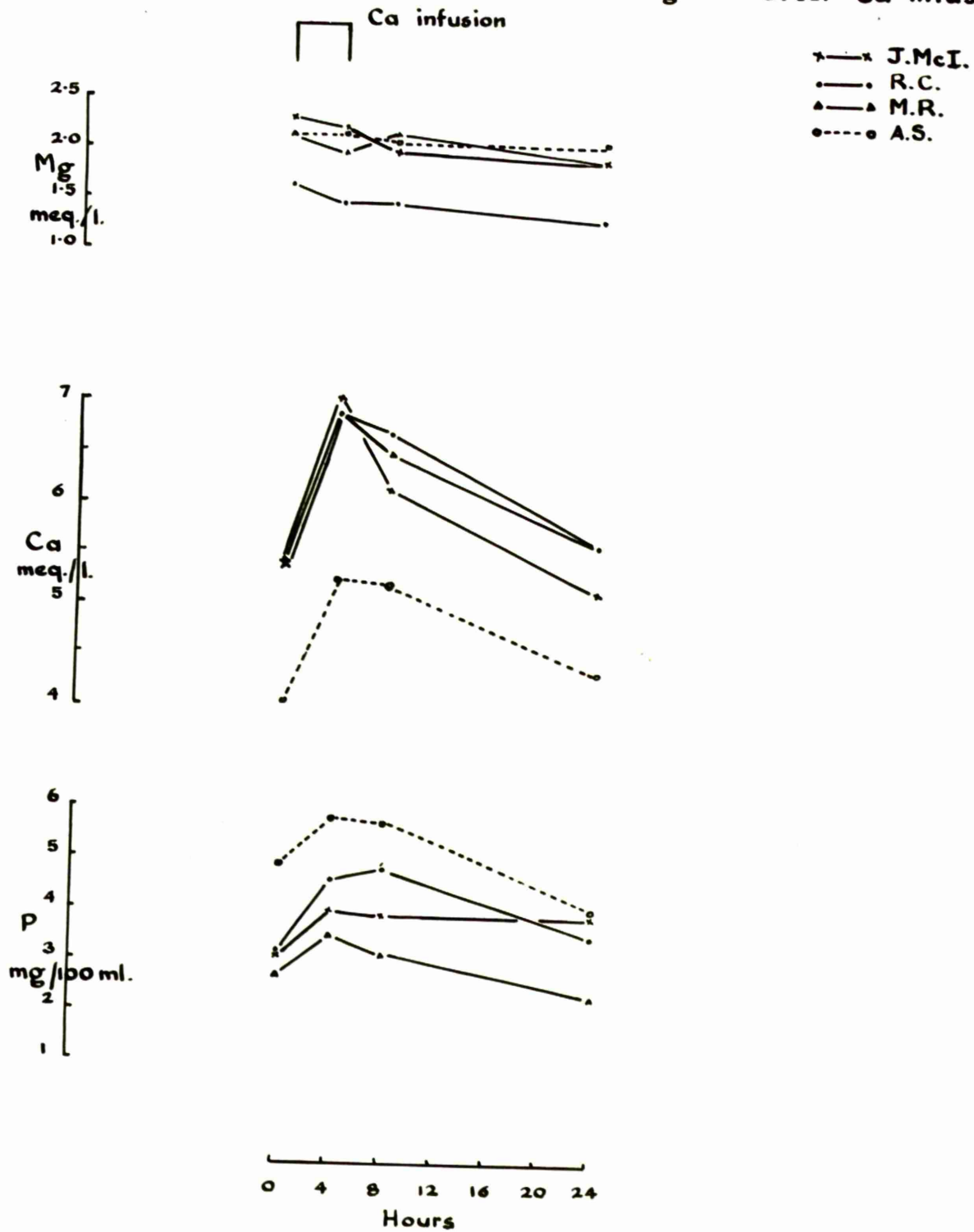
To evaluate the relationship of Mg to Ca and P, serum Mg was estimated in patients with renal calculi, in whom serum Ca and P were being determined for the differential diagnosis of hyperparathyroidism (Section IV). This was done in 10 patients, 8 of whom had a serum Ca over 5.25 meq./l., although in only 3 was it over 5.5 meq./l. P was normal in each case (2 with less than 3 mg./100 ml.). 2 had a raised blood urea, both these being the ones with normal Ca. In all these patients the serum Mg was normal. However, as the changes in Ca and P levels were so small, any effect they might have on Mg was probably not noticeable. Examples are given in Table V 1a.

Higher Ca levels were obtained during the four calcium infusion tests, during which Mg was also estimated. The serum results are given in Figure V 1. In two, the Mg levels were depressed 24 hours after infusion, also in the third which however showed a slight rise at 8 hours. It did/

TABLE V 1. Examples of serum magnesium and other electrolytes in various conditions.

<u>Patient</u>	<u>Date</u>	<u>Mg</u>	<u>Ca</u> <u>meq. /l.</u>	<u>HCO₃⁻</u>	<u>K</u>	<u>P</u> <u>mg. /100 ml.</u>	<u>B.U.</u> <u>/100 ml.</u>
<u>1a. Renal calculi & hyperparathyroidism.</u>							
E.R.		1.65	5.4			2.8	21
G.W.		2.15	5.65			3.0	41
T.C.		1.8	5.35			3.5	37
C.C.		1.75	4.8			4.0	71
<u>1b. Uraemia.</u>							
W.L.		2.15	4.55	19	5.3	6.3	222
R.N.		2.6	4.2	13	6.6	9.3	250
E.R.		3.0	4.25	17	5.6	10.1	270
J.F.		3.3	3.0	19	7.9	12.9	360
J. McC.		1.4	3.4	23	4.3	5.7	108
<u>1c. Chronic acidosis.</u>							
R.C.		2.0	4.2	12	2.1	3.2	132
J.C.	5/12	3.15	5.85	12	2.2	-	95
	11/12	2.4	-	26	2.3	-	90
	17/12	2.15	4.35	30	4.1	-	36
W.A.	11/8	2.05	6.6	9	4.2	4.9	89
	16/8	1.8	5.0	24	3.1	1.7	79
J.R.	22/11	2.4	4.7	21	4.4	-	44
	26/11	2.25	4.8	27	5.6	-	61
M.I.	14/11	2.55	4.75	24	2.0	-	150
	21/11	2.5	4.65	21	4.1	-	85
<u>1d. Alkalosis.</u>							
J.A.		4.1	-	36	3.5	-	152
W.S.		2.3	4.6	30	4.0	-	106
P.C.		1.9	4.1	41	2.4	-	57
C. McL.	27/7	2.4	-	39	3.8	6.1	150
	30/7	3.45	-	29	4.9	7.7	333

Fig V1. Serum Mg, Ca, and P during and after Ca infusion.



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did not reciprocate the Ca directly, all of which were at their highest at the end of the 4 hour infusion. The P levels, although they varied significantly did not rise much above normal levels. It is to be noted that in A.S. the idiopathic hypoparathyroid patient, the Mg was virtually unchanged; the serum Ca was not as high in this case though; in fact it did not go above normal levels, but as it was low at the beginning of the test, the actual increase was comparable. The P on the other hand was definitely above normal all the time.

V B2. Serum magnesium, calcium and phosphorus in patients with uraemia.

Another aspect of this problem may be studied in patients with uraemia, as in these cases the plasma P is very high and the Ca consequently depressed, a condition resembling hypoparathyroidism but which may lead to secondary parathyroid hyperplasia. Serum Mg was therefore estimated in all available patients, 23 altogether, 13 of whom had a raised serum Mg. The P was raised in all, in several to very high levels and in the latter the Mg was particularly high. Calcium was depressed in 16, and in the remaining 7, the P levels were not so high and the Mg was mostly normal/

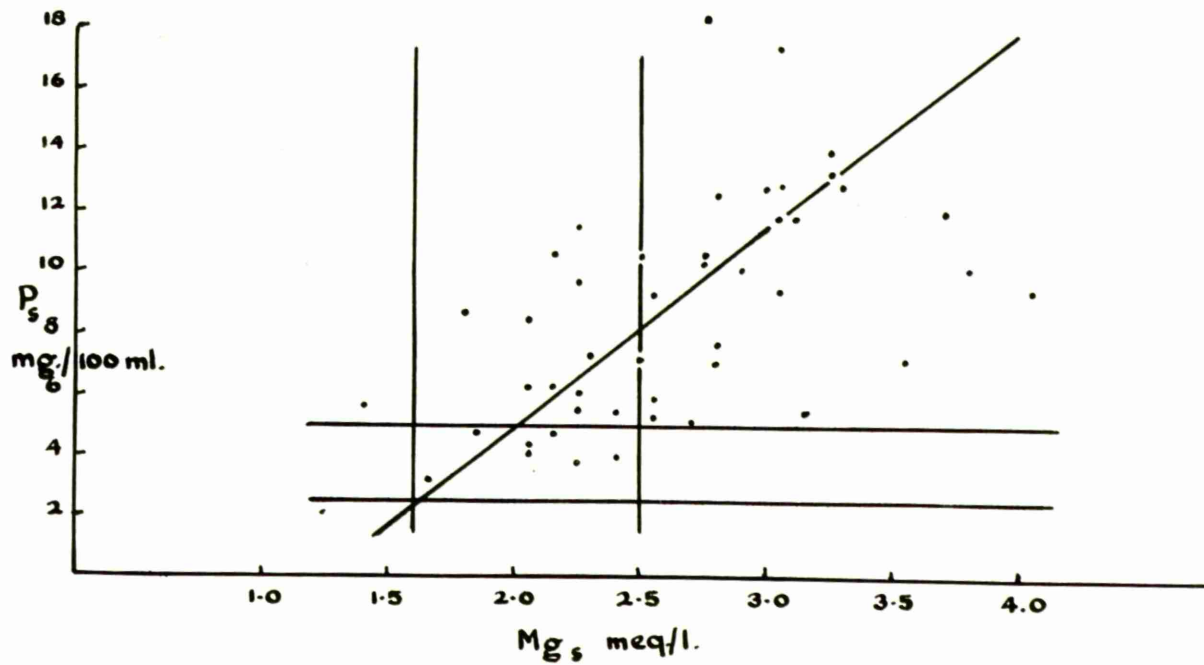
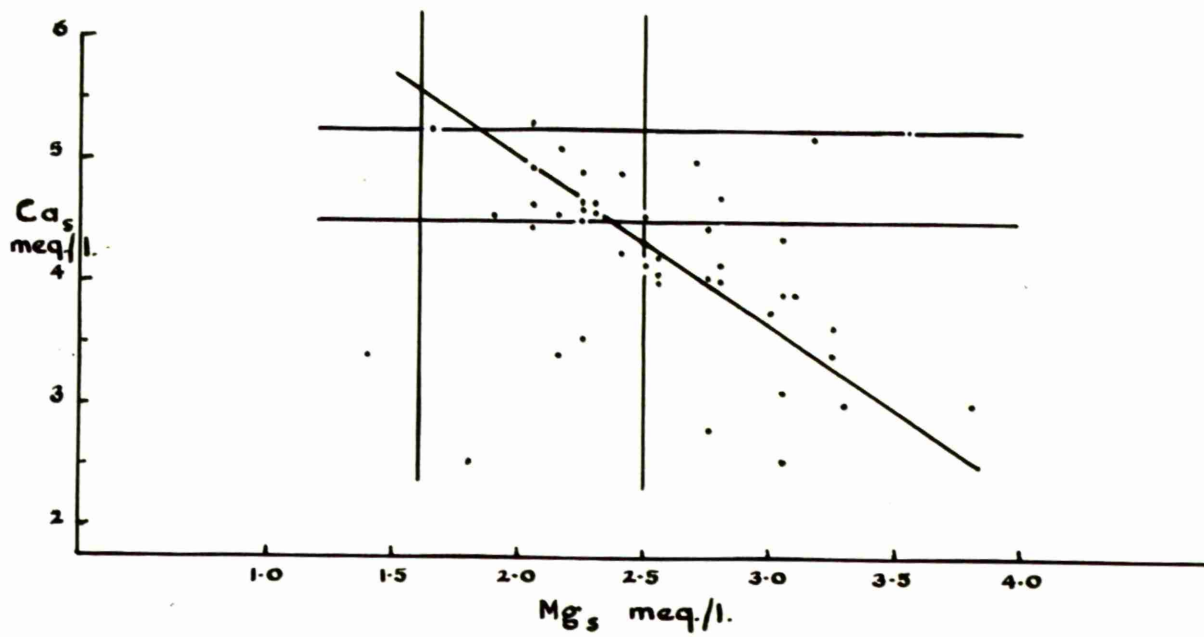
normal. Examples are given in Table V 1b. A low Mg was present in one case, J.McC., along with a low Ca, but P only slightly raised (Table V 1b). 7 other uraemic patients with a very high urea also had high Mg, but no other estimations were done at the time. Thus the cases in which there was the most severe renal retention as judged by the plasma phosphorus, were the ones which on the whole had the highest Mg and lowest Ca. (Figure V 2).

V B3. Serum magnesium in relation to acid-base balance.

Although the serum P and Ca are altered in renal failure and Mg is raised in many of these, there is such a general disturbance of electrolyte metabolism that other factors may also play a part. The usual abnormalities are an acidosis, a high plasma K, and Na and Cl are also generally low; all this is discussed in Section III. In the group of uraemic patients mentioned in the previous paragraph, as might be expected all had a lowered bicarbonate, and two-thirds had a high K, whether the Mg were raised or not.

Magnesium was estimated in some of the patients with ureteric transplants, so that the effect of prolonged electrolyte disturbance could be investigated without extreme/

Fig V2. Serum Ca, P, and Mg in uraemia.



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NUMBER			

extreme renal failure. Two of these had normal electrolytes and a normal Mg. 5 others were all admitted with symptoms of imbalance, 3 with a severe acidosis (Table V 1c). Patient R.C. had a severe acidosis and a very low plasma K, but the Mg was normal; he died the following day of hypokalaemia, so that in this instance of prolonged acidosis and K deficiency, Mg was not noticeably disturbed in the E.C.F. In patient J.C. who had similar blood results, there was a definitely increased Mg, which fell to normal as the acidosis improved, although the plasma K did not rise until a few days later. W.A. had the most severe acidosis but the K was normal until the acidosis was corrected when it fell considerably; Mg was within the normal range all the time, although it also decreased slightly as the acidosis improved. J.R. did not have nearly so severe an acidosis nor was the K abnormal, M.I. however had no acidosis, only a very low K; Mg was slightly above normal and decreased very slightly as the K was restored.

Serum magnesium was estimated in 4 patients who had an alkalosis due to intestinal obstruction with vomiting or on gastric suction (Table V 1d). Mg was raised in one, who/

who also had a low K_p , but it was normal in two others who also had a hypokalaemia. C. McI. developed renal failure latterly, so that a renal acidosis was superimposed on the alkalosis; Mg, K and P all increased as this developed.

These examples are too few to come to any definite conclusions, but it would appear that the Mg tended to be high in acidosis, or at least it decreased as the acidosis improved, while in the 4 with alkalosis, with one exception it was normal. There seem to be no obvious correlation between the serum Mg and K, a raised or normal Mg occurring with a high K in the uraemic patients, and also with a low K in the transplants with acidosis, or in patients with alkalosis.

V B4. Magnesium and electrolyte changes in the post-operative period.

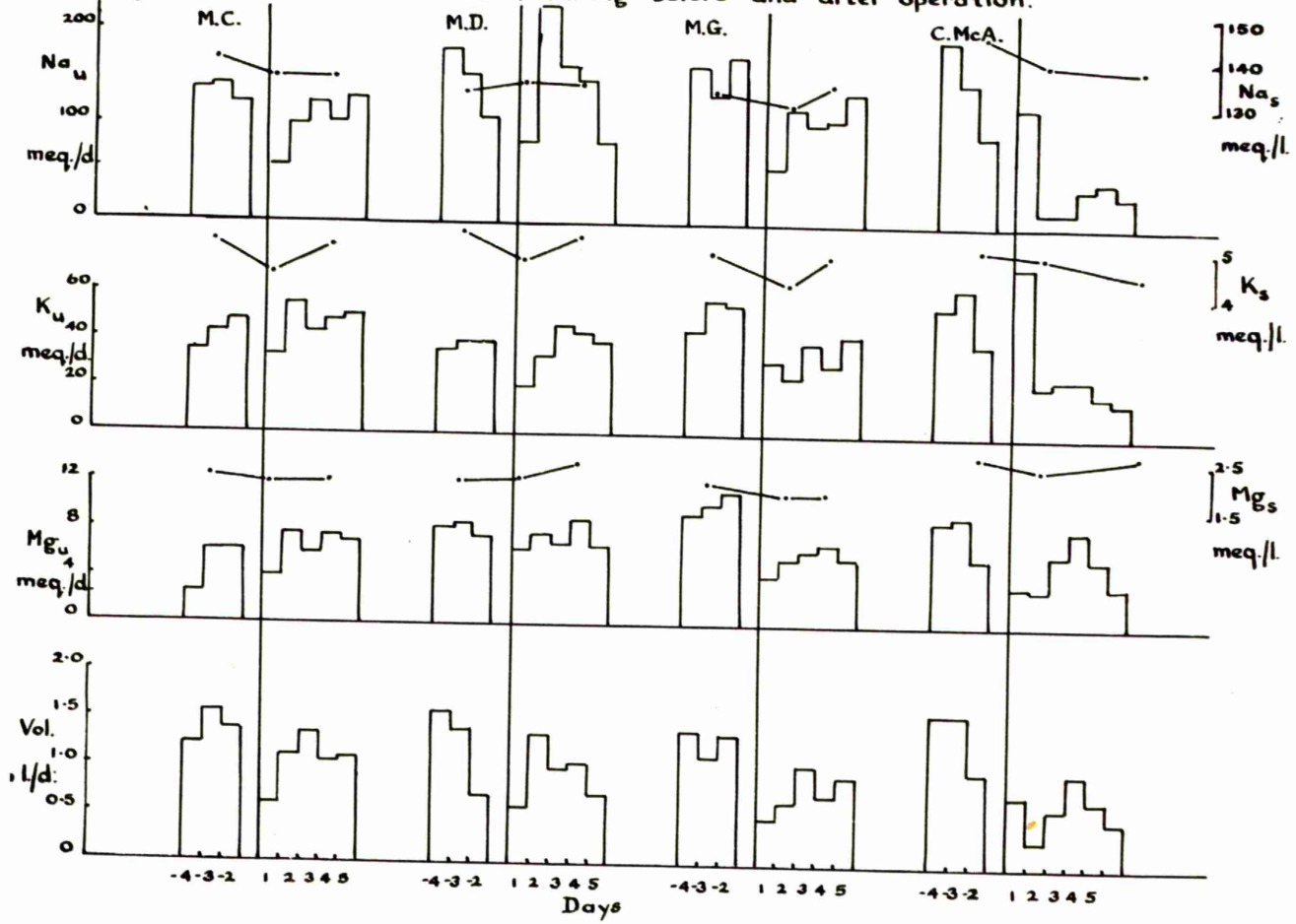
Certain electrolyte changes take place in the first few days following operation, due mainly to the action of adrenal hormones. No marked disturbance of magnesium had been defined, so this was investigated next. 5 out of 6 patients had a decreased serum Mg 24 hours after operation, but in 3 of these the change was so slight as to be scarcely/

scarcely significant. The urine excretion of Mg, Na and K was estimated in 2 of these, 24 hours before operation and 24 hours immediately after. One showed a marked fall in Na excretion, with the corresponding outpouring of K, but the amount of Mg lost was the same on both days. In the other patient, the urinary Na was much reduced again but there was less change in the K, while the Mg was very slightly decreased.

These figures were not sufficient to show any marked alterations, but it was felt that it would be worth while doing more extensive trials. Gynaecological patients for D. and C. were chosen as it was thought that they would have the least number of other disturbing factors. 8 were done altogether, urine being collected for 3 days prior to operation, and for 5 days afterwards, since the post-operative stress is generally over by then except in major operations followed by complications. The results are graphed in Figure V 3.

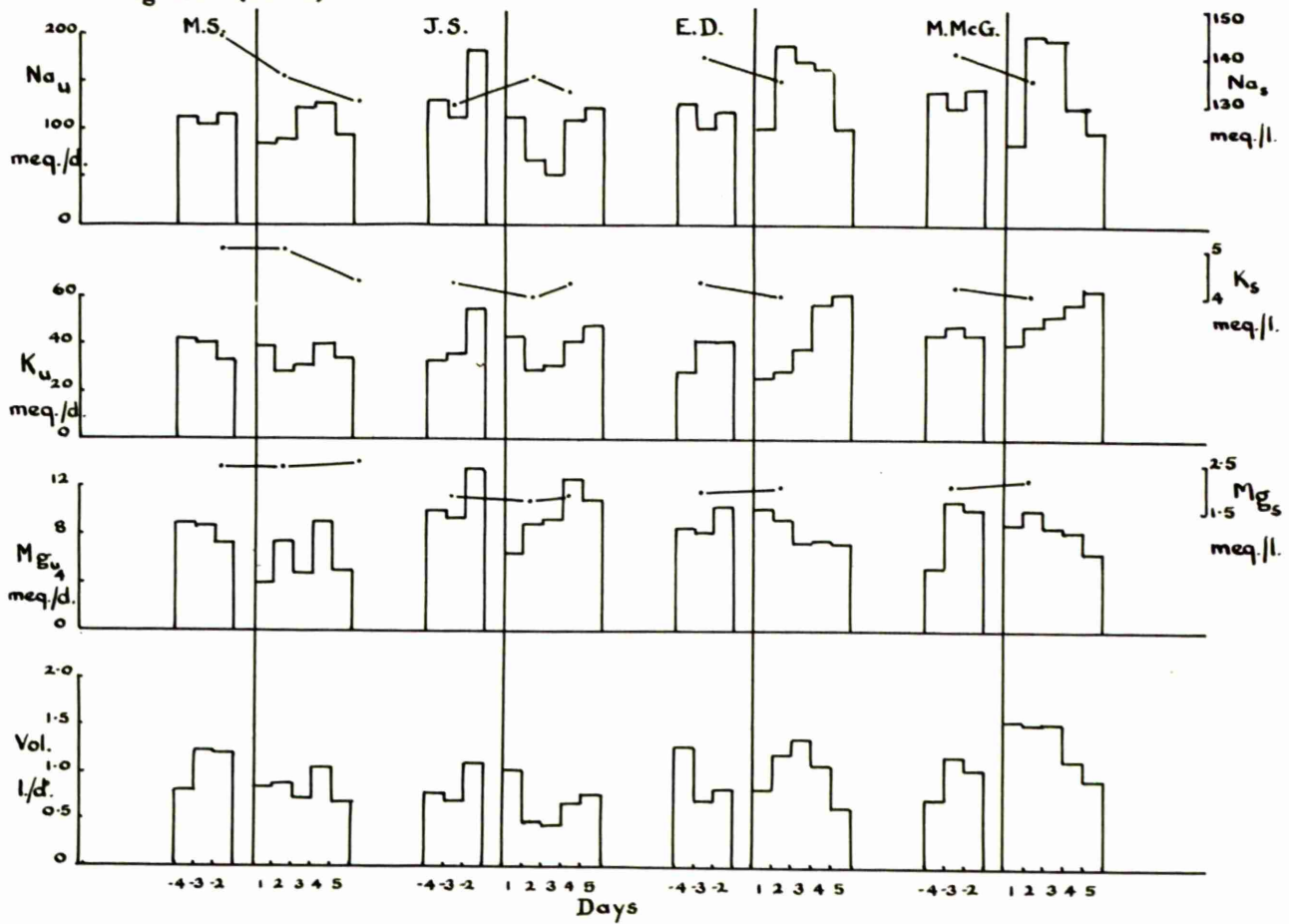
The urine Mg excretion fell below the pre-operative levels the first day in all except E.D., though only very slightly in M. McG., and M.D. Thereafter it tended to rise, except in E.D. and McMcG., but apart from the first day the amounts/

Fig 53. Serum and urine. Na, K, and Mg before and after operation.



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Fig 53. (Cont.)



I.C.D. INDEX	DIAGNOSIS	
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amounts excreted were not greatly different from the pre-operative variation. Na excretion was also less on the first day post-operatively in all except C. McA., though in several the decrease was not very marked, and a definite increase on the 2nd - 4th days was only obvious in 3 (M.D., E.D., and M.McG.). The urine volume changes were not very consistent, though the tendency was to a retention post-operatively; in general though, the Na excretion was roughly parallel to the water excretion. There was no immediate K diuresis except in C. McA., who was also the only one with much K retention later. In comparison with the Na and K variations, Mg did not appear to parallel one or the other. In M.D., C.McA. and J.S., the K excretion was roughly similar to Na, but Mg was unlike either. In M.S., E.D., and M.McG., all 3 were dissimilar, while in M.C. and M.G. all three were roughly the same.

In the plasma, both K and Na fell the first day after operation in most cases, but variations were more or less within the normal limits. Mg was virtually unchanged in all, showing only very minor fluctuations.

None of these patients showed the complete picture of/
of/

of post-operative stress, and in general the day-to-day variations were not markedly different from the three pre-operative days. One may assume then that in these instances the stress was not very great, and if it was not sufficient to produce marked changes in Na and K, it is hardly surprising that the more stable Mg showed no specific changes.

V B5. Endocrine control of magnesium.

The usual changes in electrolyte excretion following operation are to a large extent due to the liberation of ACTH, with an increased production of adrenal hormones. Results are given here in 5 patients to whom ACTH was given, either an intravenous infusion, or as ACTH gel. This should give results analogous to the effect of operation. Urine was collected for 24 hour previously, and for 24 hours of the test day (Table V. 2).

W.M. and J.S. were hospital patients who had no obvious endocrine abnormality; in J.S. there was a marked increase in the 17-ketosteroid and K excretion, and a decreased urine volume but the typical Na retention was not present; in this case Mg excretion increased slightly in about the same proportion as sodium. W.M. did not show such/

TABLE V 2. Urine magnesium, sodium, and potassium in patients given A.C.T.H.

<u>Patient</u>	<u>Urine vol. ml./d.</u>	<u>Mg meq./d.</u>	<u>Na meq./d.</u>	<u>K</u>	<u>17-Ketosteroids mg./d.</u>	<u>Remarks</u>
W.M.	1700	10.2	90	51	28	M. "Normal" A.C.T.H.
	1000	20.0	117	67	23	
J.S.	920	5.1	124	35	12	F. "Normal" A.C.T.H.
	730	7.3	187	91	41	
M.C.	1490	6.6	243	58	5.6	F. Addison's A.C.T.H.
	1070	5.0	149	81	11.0	
M.B.	1630	4.3	96	51	2.8	F. Simmonds' A.C.T.H.
	1680	3.6	126	64	1.7	
A.R.	840	8.7	211	30	7.5	M. Addison's A.C.T.H.
	770	6.5	145	51	5.5	

TABLE V 3. Three day average urine magnesium, sodium and potassium in three patients with endocrine disorders.

<u>Patient</u>	<u>Urine vol. ml./d.</u>	<u>Mg</u>	<u>Na meq./d.</u>	<u>K</u>	<u>Remarks</u>
J.D.	1160	2.3	114	21	F. Simmonds'
M.W.	3310	12.0	281	55	F. Simmonds' On Hg diuretic
	402	2.0	8	12	Diuretic stopped
	1560	4.0	175	29	On cortisone and thyroid hormone.
M.McF.	1680	11.8	236	51	F. Cushing's

such a typical response, as there was little change in the ketosteroids, sodium or potassium, but the Mg however doubled itself. In M.C., in whom the diagnosis of Addison's disease was doubtful and later disproved, on the day of the test all the typical changes were present, including Na retention, and in this case there was a decreased Mg excretion. Similar results were obtained in A.R., another Addison's, but this time there was no increase in ketosteroids, although judging by the electrolyte variation, there had been some response.

Again the results are not very definite. In the 2 patients where the ACTH had most effect as judged by the steroid excretion, urine Mg increased in 1, decreased in the other; while one in whom there was least effect showed the biggest alteration in Mg. In 4 out of 5 though, the Mg did parallel the Na excretion, rather than K.

The average urine excretion over 3 days of the three cations is also given in Table V 3, for 3 patients with various hormone disturbances. In two patients with Simmonds' disease, J.D. was untreated, and had a lower level of urinary Mg than any of the previous patients. It was similar in M.W. once her mercurial diuretic was stopped/

stopped; later, after treatment with cortisone and thyroid hormone for 9 days, it had increased, but so also had the Na and urine volume from their previous very low values. The patient M.M.P. with Cushing's syndrome on the other hand had a higher than average urinary excretion of Mg.

In the few patients with hormonal disturbance in whom it was investigated, the serum Mg was not grossly altered (Table V 4). It was highest in a patient with Cushing's syndrome, but the patient with Simmonds' disease also had a serum magnesium at the upper limit of normal. The others all had a normal Mg, the lowest being the Addisonian. In W.M. the Mg was slightly higher after the ACTH infusion although was still normal, but as mentioned in the previous paragraph, he was perhaps not typical.

TABLE V 4. Serum magnesium in some patients with endocrine disorders.

<u>Patient</u>	<u>Mg meq./d.</u>	<u>Remarks</u>
M.G.	1.70	M. Addison's
J.D.	2.55	F. Simmonds'
J.B.	2.30	M. Bilateral adrenalectomy for hypertension. Treated with cortisone.
H.W.	2.70	F. Cushing's
W.M.	1.90	M. "Normal"
	2.15	A.C.T.H.

SECTION V. MAGNESIUM METABOLISM IN VARIOUS ELECTROLYTE
DISTURBANCES.

V C. Discussion.

V C1. General.

In the results presented here, there were no clear-cut alterations in the behaviour of magnesium under fairly varied conditions. There were not really sufficient numbers where all conditions were comparable for definite conclusions to be drawn, although some trends were apparent. In some cases there was apparently little alteration in surrounding conditions and a fairly marked change in magnesium levels, while in other instances there was a wide variation of electrolyte and hormone balance with comparatively little effect on magnesium.

V C2. Relationship of magnesium and calcium.

In the serum the tendency was for calcium and magnesium to react in opposite directions. Where serum calcium was raised abruptly by infusion, serum magnesium was depressed, while in the ureemias, serum magnesium was raised and calcium was lowered. In the latter, plasma phosphorus was markedly increased, but it was also increased after the calcium infusion, so that the magnesium levels did not appear/

appear to be affected primarily by phosphorus levels. This agrees with other findings, for example, Schmidt & Greenberg (1935), Brookfield (1937).

V C3. Relationship of magnesium to other electrolytes, including post-operative and adrenal changes.

There did not appear to be any direct correlation between serum magnesium and potassium levels. In the uraemias, both were increased, while in prolonged potassium deficiency with low serum potassium, magnesium was normal or high. In the 8 post-operative cases there was very little change in magnesium although potassium fell appreciably immediately after operation.

In the post-operative cases there was no regular correlation either between magnesium and potassium or sodium excretion, all these apparently varying independantly. However, none of these showed all the usual post-operative alterations, so that it is possible that the changes were too slight to affect magnesium much. The one who did show the most typical sodium and water retention followed by diuresis (M.D.) was the one who showed least alteration in magnesium excretion. Levey et al. (1956) also Martin et al. (1950) found that post-operatively magnesium levels depended/

depended more on the intake relative to losses than on the action of adrenal hormones. In the cases here losses were relatively slight, and the patients were eating normally soon after operation.

In the patients who were given ACTH there was again no regular pattern. In the one who showed the most complete response, urine magnesium decreased, but in another in whom there was apparently little response it rose markedly. The magnesium excretion did tend to follow sodium rather than potassium excretion. Haynes et al. (1952) also found this, although his figures too are somewhat variable. Hills et al. (1955) also found magnesium excretion unrelated to potassium, but that ACTH decreased magnesium excretion.

V C4. Effect of changes in acid-base balance on magnesium.

Again the results were not very conclusive, although considerable deviations of acid-base balance were encountered. In the uraemic cases acidosis was present in all, and although magnesium was increased in many, it was not invariable. In the patients with ureteric transplants and chronic acidosis, serum magnesium tended to fall as the acidosis was corrected, similar to potassium, although it was frequently within normal limits. However the highest figure/

figure for serum magnesium in the series was in a patient with acute alkalosis. Jabir, Roberts & Womersley (1957) found little change in serum magnesium in ammonium chloride acidosis, and Barker, Elkinton & Clerk (1959) also found that in acute experiments that blood and urine pH had little effect on magnesium levels.

V C5. Magnesium in renal failure.

The most consistent alteration in magnesium levels was the increase in serum in renal failure. All the electrolytes are affected in these cases so that it is difficult to say which has the primary effect. Robinson, Murdaugh & Pöschel (1959) state that the increase in serum magnesium in renal failure is a result of decreased G.F.R. rather than the effect of acidosis, reciprocal action of calcium, or increased potassium.

V C6. Reasons for apparent stability of magnesium levels.

Magnesium occupies a place physiologically somewhere between calcium and potassium. Like calcium, to which it is chemically similar, there are relatively large amounts in bone, so that factors which affect bone deposition and resorption would be expected to alter magnesium levels in serum and urine. On the other hand, like potassium it is one/

one of the main ionic constituents of tissue cells, and the amount circulating in the E.C.F. is only one-tenth of that in the tissues, so that it only requires a small amount of tissue breakdown to release significant amounts of magnesium; if renal loss is small as in renal failure with anuria it will result in increased amounts in the serum, as it does with potassium. Although in the kidney, as magnesium is a divalent ion, it is probably handled by the tubules more like calcium than like the monovalent ions, which is possibly why the effect of ACTH and adrenal hormones is not so distinct.

Again like potassium, if losses are prolonged, for example, after operation, it may or may not be shown up in the serum because of the large body stores. But magnesium has two large reservoirs, bone and tissue, which may "buffer" each other, maintaining E.C.F. levels within narrow limits although conditions may vary considerably. This probably is one of the reasons why it is so difficult to get consistent unequivocal results unless as many factors as possible are strictly controlled, which owing to the nature of clinical material available here was rarely possible.

SECTION VI. FACTORS AFFECTING BLOOD CELL POTASSIUM.

VI A. Introduction.

VI A1. Potassium distribution in the body and its estimation.

Potassium is most commonly estimated in the serum, which is a measure of its concentration in the extracellular fluid, but this contains only 2% of the total amount of potassium in the body, as compared with 80% for sodium. Increase or decrease in the extracellular levels has a profound physiological effect, although quantitatively the change in the total amount circulating may be very slight. Particularly in renal disease where the normal renal control is impaired, it is important to know the potassium requirements of the whole body, not just one small compartment. This can be approached in three ways: directly by actual estimation in the tissues from biopsy specimens, which is not very practicable as a routine test; indirectly, by balance data, which may be done in special cases, but is time consuming and requires several days before the whole picture is obtained; and lastly by estimation of blood cell potassium, on the assumption that/

that this is an indication of the state of the tissue cells as a whole. It is with this last assumption that this section is mainly concerned.

VI A2. Occurrence of low blood cell potassium levels.

A few investigations of blood cell potassium (K_c) have been carried out, but no comprehensive picture has really been established. A low K_c has been reported in several clinical conditions, for example diabetic acidosis (Guest 1942, Danowski, Hald & Peters 1947, Nichols & Nichols 1953), uraemia (Hoffmann & Jacobs 1933), chronic potassium deficiency (Talbot 1941), and untreated Addison's disease (Hatt 1952). It has also been reported as being low in Cushing's disease, in association with a hypokalaemic alkalosis (Eliel & Pearson 1951). A potassium deficiency is very often associated with these conditions.

VI A3. Relationship between blood cell, plasma and tissue potassium.

It is now well recognised that plasma potassium does not necessarily reflect the state of body stores of potassium, as it can be high, normal or low in potassium deficiency, depending on the conditions of development. It has been found also that there is no good correlation between/

between plasma potassium and K_o (Hutt 1952, Lens, Stein & Meyer 1952). From balance data Eliel & Pearson (1951) and Hutt (1952) found that a low K_o indicated potassium deficiency, although Straeten & Ward-McQuaid (1952) found normal K_o values in some deficiency states. Generally speaking, most authors have found a low K_o to be associated with a potassium deficiency, but a normal K_o does not preclude a deficiency, even of considerable magnitude (Hegmauer 1943, Nichols & Nichols 1953, Knowles, Alverson & Rubinstein 1955). Davidson & Kjerulf-Jensen (1950) state that a low K_o is unusual in potassium deficiency, but give no data. In some experimental studies on potassium deficient animals, tissue analyses were carried out as well as K_o estimations. Cotlove et al. (1951) found both low K_o and low tissue potassium when depleted of potassium.

VI A4. Other factors affecting cell potassium.

Apart from potassium deficiency due to inadequate intake, potassium is also lost from the cells in starvation and dehydration, and K_o was low in these instances (Nichols & Nichols 1953). It was also low in salt deficiency (McCance 1937), and hypotonicity, as reflected by a low plasma/

plasma sodium (Hoffmann & Jacobs 1933, Knowles et al. 1955), while Maizels (1954) found potassium uptake by cells in vitro decreased when plasma sodium was low although tonicity was maintained with lithium. Hutt (1952) however found no correlation between plasma sodium and K_c .

Very few of these reports are concerned with urological diseases, and as a considerable amount of electrolyte variation is found in these patients, it was thought that it would be worth while investigating the behaviour of blood cell potassium under these different conditions.

SECTION VI. FACTORS AFFECTING BLOOD CELL POTASSIUM.

VI B. Results.

VI B1. Variations in blood cell potassium.

Blood cell potassium (K_c) was estimated in many of the patients discussed in the previous sections. Results from 178 tests have been analysed; about half of these were from repeated tests in the same person as conditions were altered. The variation in K_c with plasma K (K_p), Na, and acid-base balance has been tested statistically in these examples. The distribution is given in Table VI 1. For those with a low K_c , the plasma K was significantly higher and the plasma Na was significantly lower than in those with a normal K_c (Table VI 1a and b). Also the plasma bicarbonate was lower (Table VI 1c); this was taken as an indication of acidosis, of metabolic or renal origin, as none of these particular patients had a primary respiratory disturbance. As for those with a high K_c , the reverse was not significant except in the case of Na. A few representative examples have been given for the various types discussed below, rather than listing the entire mass of figures (Table VI 2).

VI B2. Correlation of blood cell with plasma potassium.

It will be seen from the table VI 1a that although the

K_p

TABLE VI 1. Numbers of blood analyses correlating K_c with plasma K , Na and HCO_3^-

	<u>Normal K_c</u>	<u>High K_c</u>	<u>Low K_c</u>	<u>Total</u>
<u>1a. K_c and plasma K.</u>				
Normal K_p	80	15	10	105
High K_p	12	1	8	21
Low K_p	<u>40</u>	<u>8</u>	<u>4</u>	<u>52</u>
	<u>132</u>	<u>24</u>	<u>22</u>	<u>178</u>
Mean K_p (meq./l.)	4.4±0.8	4.2±0.6	5.2±1.3	
<u>1b. K_c and plasma Na.</u>				
Normal Na_p	78	20	5	103
High Na_p	3	-	-	3
Low Na_p	<u>51</u>	<u>4</u>	<u>17</u>	<u>72</u>
	<u>132</u>	<u>24</u>	<u>22</u>	<u>178</u>
Mean Na_p (meq./l.)	135±6.3	138±4.1	124±10.6	
<u>1c. K_c and plasma HCO_3^-</u>				
Normal HCO_3^-	62	19	4	85
High HCO_3^-	2	-	-	2
Low HCO_3^-	41	3	16	60
Hyperchloraemic acidosis	<u>27</u>	<u>2</u>	<u>2</u>	<u>31</u>
	<u>132</u>	<u>24</u>	<u>22</u>	<u>178</u>
Mean HCO_3^- (meq./l.)	22.4±4.6	24.2±4.3	18.6±5.8	

K_p was statistically higher in those with a low K_o than with a normal K_o , this is not to say that with a low K_o normal or low values of K_p were not occasionally obtained, but the higher ones outweighed these by their greater deviation from normal. On the other hand with the high K_o group, although it was not statistically significant, the K_p levels tended to be normal or low, and only one was high. In a number of cases then, the blood cell K was inversely reflected by the plasma K, in other words, a movement between E.C.F. and cells was apparent. However, this is by no means a general rule since an abnormal K_p was frequently present with a normal K_o (52 out of 132 tests or 39%), or a normal K_p with an abnormal K_o (25 out of 46 or 54%). Other factors obviously influence the distribution of which two are considered below.

VI B3. Effect of tonicity.

In the absence of direct measurement, a rough guide to the tonicity of the E.C.F. may be given by estimation of plasma Na, since this is one of the main components of the E.C.F. in determining tonicity, just as K is one of the main components in the intracellular fluid, other osmotically active substances such as glucose and urea being equally dispersed/

dispersed in the two phases. In order to maintain osmotic equilibrium the cell K might be expected to alter with changes in extracellular Na. From the Table VI 1b it can be seen that practically all those with a low K_o had a low plasma Na and tonicity was thereby maintained on both sides of the membrane but at a lower level. Although those with a high K_o did not apparently have an abnormally high plasma Na, they were nevertheless significantly higher than the group with a normal K_o , which included a fairly large proportion with plasma Na below normal. Actually hypernatremia was very rare in this particular series of patients. Examples are given in Table VI 2a.

VI B4. Effect of acid-base balance.

These patients were all urological cases so a degree of acidosis was present in a considerable number, in fact plasma bicarbonate was below normal in over half the total number of analyses. It can be seen from Table VI 1c that while 51% of those with a normal K_o had a lowered bicarbonate, this compares with over 80% of those with a low K_o , this being statistically significant. K_o was examined in only two patients with alkalosis, so that no definite conclusions may be drawn about this condition; it may be significant that/

TABLE VI 2. Examples of K_2 and plasma electrolytes.

<u>Patient</u>	<u>P.C.V.</u>	<u>K_c</u>	<u>K</u>	<u>Na</u>	<u>Cl</u>	<u>HCO_3^-</u>	<u>B.U.</u>
	<u>%</u>		<u>g</u>	<u>meq./l.</u>			<u>mg%/100 ml.</u>

2a. Effect of tonicity.

M.O.	39	80	4.2	116	66	21	20
	36	84	3.5	128	78	22	25
S.R.	36	75	4.4	100	60	19	100
D.S.	36	85	4.0	120	79	22	310
I.S.	37	106	3.8	147	111	21	47
W.McL.	20	105	4.4	148	104	22	28
J.L.	38	104	5.1	143	98	23	160

2b. Acute acidosis.

W.F.	47	94	6.6	125	87	13	171
E.M.	17	99	6.4	147	98	2	480
P.McD.	40	91	6.1	122	88	16	207
W.S.	49	79	5.8	139	88	17	124
H.R.	38	89	7.6	134	98	16	189
C.B.	29	79	7.8	119	74	14	194

2c. Acute alkalosis.

W. McC.	45	104	4.9	139	88	30	116
C. McI.	36	104	4.2	129	77	37	100

2d. Chronic acidosis.

W.H.	52	93	5.0	147	114	17	74
C.T.	44	95	4.3	145	112	16	70
G.D.	46	102	4.4	140	113	18	50

TABLE VI 2. (Contd.)

Patient	P.C.V. %	K _o	K _p	Na meq./l.	Cl	HCO ₃	B.U. mg./100 ml.	Treatment ⁺
<u>2c. Correction of chronic acidosis.</u>								
R.M.			3.9	148	116	6	160	52 meqs.K in 2 days.
	40	89	2.0	147	115	17	143	104 meq. K in 2 days
	40	98	2.6	147	110	28	95	432 meqs.K in 6 days
	37	100	4.9	146	111	27	61	
P.W.	28	96	4.7	142	112	17	390	No K given.
	29	104	3.6	142	99	22	550	
W.A.	50	93	4.4	133	112	11	88	No K given.
	40	93	2.8	135	109	18	89	162 meq. K in 3 days.
	40	95	3.6	135	108	21	48	
<u>2f. Chronic K deficiency.</u>								
M.I.	43	95	2.0	131	88	24	150	225 meqs.K in 5 days
	34	102	3.4	131	93	22	100	
	33	96	4.1	135	102	21	85	36 meqs.K in 2 days.
<u>2g. Correction of chronic acidosis with severe K deficiency.</u>								
J.C.	33	86	2.2	131	106	12	95	26 meqs.K
	31	90	2.0	130	99	19	95	228 meqs.K in 8 days.
	26	107	2.8	136	92	29	53	
	27	102	4.1	138	97	30	36	102 meqs.K in 3 days.
J.O.	37	81	1.6	135	109	14	150	78 meq. K in 1 day.
	30	92	2.2	141	108	20	160	
	34	102	4.5	133	102	19	67	228 meqs.K in 5 days.

+ K given as citrate unless otherwise stated.

that the K_c was slightly above normal in both instances (Table VI 2c).

VI B5. Interrelation of the three factors.

The particular level of blood cell potassium thus depends on several factors which may all react together or in opposition as regards their effect on cell potassium. It can be seen from the figures given above that a low K_c was associated with acidosis and hypotonicity, and although sufficient figures were not available for alkalotic and hypertonic conditions, the K_c did tend to increase in the few cases observed.

A fourth factor may be added, that of time, as different results were obtained ⁱⁿ acutely and chronically ill patients. In acute renal acidosis the plasma potassium was generally high; thus 18 of the 21 cases with raised plasma K came in this category; 10 had a normal K_c , in 8 it was low (Tables VI 2b,3). On the other hand in chronic acidosis, plasma K was normal or low and K_c normal, plasma Na also being generally normal; this was true of 27 of the 31 patients with ureteric transplants and chronic hyperchloraemic acidosis (Table VI 2d). But these apparently normal results masked a considerable body deficiency which only became obvious when the acidosis was corrected.

VI B6./

VI B6. Unreliability of blood cell potassium as a guide to tissue levels.

Results from some of these chronically and acutely ill patients have been presented in Section II and III, and give additional evidence as to the state of body stores of potassium. For example in the patients with acute renal failure and up to 6 days anuria where potassium loss was obviously minimal, K_c was nevertheless low while plasma K was high, and this divergence increased as the patients' condition deteriorated (e.g., Table III 1, C.B.) or returned to normal as diuresis set in and the patient improved (e.g., Table III 1, M.C., H.R.). In these cases the low K_c did not reflect an overall deficiency in the tissues since there were little or no losses, but rather an alteration in distribution between the intracellular and extracellular phases; in addition some dilution was taking place due to the retention of metabolic water. It was also noticed that in one of the cases on anabolic steroids (Table III 1, R.N.) these changes were minimal.

On the other hand, the patients with ureteric transplants and chronic acidosis in many cases had an underlying tissue deficiency with apparently normal results. For/

For example in Table II 4, W.A. (b) and (c) and P.W. (a) all had normal cell and plasma K on admission, but plasma K dropped immediately the acidosis was corrected and required up to 200 meq.K to restore it to normal, K_o meanwhile being little changed. J.C. and J.Q. (Figure II 9 and 10) both had severe acidosis and potassium depletion, and K_o was also low. They required 140 and 130 meq.K respectively before K_o became normal, and a further 360 and 520 meq.K before the plasma K also returned to normal.

If a low K_o is found in conjunction with a low plasma K it is probable that there is a deficiency of potassium in the body. If there is also an acidosis present it is likely to be of considerable magnitude. However, a normal K_o does not necessarily prove the absence of a deficiency.

VI B7. Tissue potassium.

Tissue analyses were possible in only 3 instances (Table VI 4). R.C. was an old ureteric transplant patient who was presumed to have died as a result of potassium deficiency, as apart from pyelonephritis nothing significant was found at post-mortem. The results for skeletal muscle potassium supported this hypothesis, but 12 hours before death, although plasma K was very low, K_o was only at the lower/

TABLE VI 4. Tissue potassium.

<u>Patient</u>	<u>Skeletal muscle</u>		<u>Last blood results</u>				<u>B.U. mg./100 ml.</u>	
	<u>K meq./Kg. wet tissue</u>		<u>Na</u>	<u>Cl</u>	<u>HCO₃⁻ meq./l.</u>	<u>K_p</u>		<u>K_c</u>
R.C.	73		146	107	12	2.1	91	
P.McD.	83		122	88	16	6.1	91	207
P.W.	100		143	106	17	3.4	103	590

Normal skeletal muscle K: average 85 meq./Kg. wet tissue.

lower limit of normal, so that in this case at least, the blood cell potassium was little guide to the tissue potassium. The cell potassium was also at the lower limit of normal in P. McD., but was high in the plasma; as the muscle analysis was normal the loss of potassium had evidently not reached significant proportions. This patient was an example of the acute acidotic type, while in B.C. and P.W. the acidosis was of long-standing duration. P.W. was also a ureteric transplant case with chronic nephritis and hyperchloraemic acidosis, and uraemia for over a month. He had been receiving a small amount of potassium citrate orally (approximately 24 meq./d.), but it is difficult to see how this could account for the figures for K_c and skeletal muscle, both of which were above normal, while the plasma K was slightly below normal.

SECTION VI. FACTORS AFFECTING BLOOD CELL POTASSIUM.

VI C. Discussion.

VI C1. General.

From these results it is obvious that too many factors influence the level of potassium in the circulating blood cells for its measurement to be of much use as a guide to potassium requirements of the body. It also accounts for the varied results in the literature. Generalised breakdown or reduction of cellular material as a result of starvation, dehydration or post-traumatic catabolism are as important in the development of potassium deficiency as actual disturbances in electrolyte balance although in recent years more attention has been given to the latter.

VI C2. Tonicity in acute and chronic acidosis.

Blood cell potassium varied most consistently with plasma sodium, in other words, maintenance of ionic tonicity is one of the most important adjustments. Hoffman & Jacobs (1933) and Knowles et al. (1955) also found this, although Nutt (1952) did not find any such relationship. This possibly accounts for the difference between the K_c in acute and chronic acidosis; in acute acidosis due to renal failure there is generally some retention of water in plasma/

plasma and cells as a result of the oliguria, and the small amount of potassium that is removed from the cells to maintain balance will remain in the extracellular fluid, thus giving the high plasma and low cell potassium observed. The low K_c and plasma sodium in these cases are not a result of deficiency as they are not improved by giving the ions, but are due to dilution, as they return to normal once diuresis starts and the excess water is removed.

On the other hand in the case of the ureteric transplant patients where the acidosis has developed gradually there is a general loss of potassium from the body, but tonicity is maintained and plasma sodium and K_c are apparently normal.

VI C3. Effect of sodium and potassium on each other.

The other factor which must be taken into account when considering sodium and potassium levels is their reciprocal action on each other. Where there is a primary potassium loss, as for example a renal tubular lesion, its place may be taken to some extent in the tissue cells by sodium (Black & Milne 1952, Fourman 1954, Evans & Milne 1954). Sodium loading can cause a displacement of potassium (Kreman et al. 1955), as for example may happen following operation when/

when relatively too much saline may be given with little or no potassium. A low potassium diet with a high sodium content will rapidly produce a low tissue potassium and extracellular alkalosis, but the same level of potassium intake and a normal ratio of sodium will not do this (Darrow et al. 1948, Meyer et al. 1950, Moore et al. 1955). Stress and adrenal cortical hormones have the same potentiating effect (Eliel, Pearson & White 1952, Moore et al. 1955). These workers noticed also that the physical effect on the patient is increased under these conditions, although the deficiency may not be any greater (Fourman 1954). On the other hand, very large potassium deficits may be present with acidosis without the patient having such severe clinical symptoms.

These effects are shown in the balance experiments here. For example in J.C. (Figure II 9), sodium was displaced from the cells during the period of strong potassium retention, for although the sodium balance was negligible, the plasma levels rose by 5 meq./l. in addition to the expansion of extracellular fluid and fall in P.C.V. In R.M. (Figure II 10) there was a considerable sodium load given, and K_c fell while plasma sodium remained unchanged.

VI C4./

VI C4. Influence of hydrogen ion on potassium.

Sodium is not the only cation to consider in relation to potassium, there is also hydrogen ion. It can also replace or displace potassium from the cells as part of the buffering mechanism (Darrow et al. 1948, Cooke et al. 1952, Orloff, Kennedy & Berliner 1953), so that in acidosis potassium tends to come out of the cells (Fenn & Cobb 1933, Black, D.A.K, 1953, Scribner, Fremont-Smith & Burnell 1955), and depending on the ability of the kidneys to excrete potassium, a deficiency may or may not develop. Also unless the acidosis is corrected at the same time potassium is not readily taken up by the cells (Scribner et al. 1955). The reverse holds in alkalosis - in many instances the alkalosis is not cured until potassium is given (Black & Milne 1952). This is not quite so much the opposite case as it may seem at first. In the former, potassium deficiency is secondary to the acidosis and accumulation of H^+ ; in the latter potassium deficiency is a primary cause, its place in the cells being taken by H^+ , giving an intracellular acidosis, but this time leading to an extracellular alkalosis (Berliner, Kennedy & Orloff 1951, Cooke et al. 1952, Gardner MacLachlan & Berman 1952 and Black & Milne 1952).

VI C5./

VI C5. Effect of hormones on potassium.

The influence of hormones, in particular the adrenocortical steroids (including aldosterone) have not been examined in great detail here, apart from mentioning briefly their effect on sodium retention and potassium deficiency. This again is possibly one of the differences between the acutely and chronically ill patients, as the stress is greater in the former. The other point at which hormones have to be considered is in the treatment of anuric patients where anabolic steroids may be used to keep potassium in the cells and to prevent the toxic rise of potassium in the plasma.

VI C6. Factors to be considered when assessing the state of body potassium.

When considering plasma and blood cell potassium results it is essential to obtain details of clinical history such as fluid balance, approximate intake of ions, assessment of losses, rate of onset, and if possible, the primary cause of disturbance. Only then can one suggest treatment. As far as diagnosing potassium deficiency from K_c results, if both K_c and plasma potassium are low it is probable that there is a fair deficiency in the body, although/

although if plasma sodium is low and overhydration is present, this may not necessarily be so. Particularly in the case of anuric or oliguric patients, it is better to wait until a reasonable urine flow is obtained before giving large amounts of potassium. If however, K_c is low, plasma sodium is normal and in addition there is an acidosis present, it may be assumed that there is a considerable deficiency, and although plasma potassium may not give any indication of this, it is advisable nevertheless to give some potassium when correcting the acidosis, and to keep a careful check on it for several days.

A body excess of potassium is a comparatively rare occurrence, but what occurs more frequently is an extracellular excess, due to liberation of potassium from the cells with impaired excretion. This can be minimised by preventing catabolism as much as possible, by giving glucose and insulin, anabolic steroids and alkalis; this is the basis of the treatment for patients with anuria. Estimation of blood cell potassium may be useful in clinical work by giving another parameter, but unless all the factors discussed above are borne in mind, it may give misleading results. In addition, normal results do not preclude body deficiencies/

deficiencies, so that its use should probably be limited to special cases where closer investigations are being carried out.

SECTION VII GENERAL SUMMARY

VII A Electrolyte imbalance in patients with ureteric transplant.

A 1. A high incidence of hyperchloraemic acidosis and hypokalaemia in patients with ureteric transplants was confirmed.

A2. This was evident any time from a fortnight after operation onwards, but after a few months stabilisation apparently took place.

A 3. In the immediate post-operative period, the usual catabolic changes were observed with sodium and chloride retention. From balance studies it was noticeable that already chloride excretion was somewhat less than sodium when their intakes were similar. Potassium concentration in the rectal fluid was relatively high (in contrast to sodium and chloride) so that once rectal drainage was established, there was danger of potassium deficiency developing, particularly when intake was poor.

A 4. Balance experiments in the patients with older ureteric transplants confirmed their relative inability to conserve potassium and to adjust its excretion under various conditions. Sodium and chloride on the other hand were adequately conserved on a low sodium salt diet, but /

but changes in their balance were not always reflected by changes in the plasma owing to the effects of volume changes and ionic transfers.

A 5. Figures for plasma electrolytes are given showing the effect of treatment on the more severely ill patients. In particular, attention is drawn to the development of hypokalaemia during correction of the acidosis. From balance experiments it was shown that very large potassium deficits were present, but were sometimes masked by the acidosis and apparently normal plasma potassium levels. The development of this potassium deficiency is discussed.

VII B. Electrolyte changes in acute renal failure and anuria.

B 1. Figures for plasma electrolytes are given in 14 patients with anuria and 2 with chronic uraemia. The urea, phosphorus, and bicarbonate were abnormal in all; calcium was lower and potassium and magnesium were higher than normal in most cases. The potassium and magnesium on the whole moved in parallel, but not invariably or to the same extent. Urine electrolytes were estimated only in 2 patients during the diuretic phase, and showed a large excretion of sodium, chloride and potassium.

B 2. The comparison of the relative levels and changes in plasma urea and phosphorus appeared to be a useful guide to/

to clinical condition and prognosis in some cases. A decrease in phosphorus sometimes indicated improvement earlier than the urea, and a moderately increased phosphorus with a high urea gave a better prognosis than a much higher phosphorus with the same urea level. Reasons for this are discussed.

B 3. Anabolic steroids were given to 5 patients. In 3 there was an improvement in urea, phosphorus and electrolyte levels which was maintained, but it was continuing the trend of the previous day. In the other 2, there was little effect although the rise in urea was momentarily halted, and the patients died. Although conditions were not always strictly comparable, the use of anabolic steroids would seem to be of benefit in the treatment of renal failure.

VII C. Biochemical tests in the diagnosis of hyperparathyroidism in patients with renal calculi.

C 1. Results for serum calcium and phosphorus from 60 patients with renal calculi are presented. Single blood estimations were found to be inadequate as deviations from the normal may be slight, and variable from day to day. The difficulties of diagnosing hyperparathyroidism in patients with renal disease are discussed and minimal criteria proposed for further investigation of parathyroid function. The importance of assessing renal function, bone involvement, acid base balance and non-ionised calcium is also mentioned, as/

as they all affect the interpretation of the results.

C 2. Urine calcium excretion on normal or low calcium diets was found to be increased in one-third of the patients in whom it was estimated, and is an important factor in the aetiology of stone formation. It was not always associated with hypercalcaemia.

C 3. A calcium infusion test was tried in 3 cases of renal calculus and in 1 with idiopathic hypoparathyroidism. In all 4 there was an increase in serum calcium and phosphorus and in the rate of phosphorus excretion immediately after the infusion. In the hypoparathyroid patient there was an increase in 24 hr. excretion of phosphorus of 54%, while in 2 of the others there was a decrease of 9 and 28%. It was felt there was not sufficient distinction between normals and border-line cases of hyperparathyroidism to warrant its inclusion as a routine test.

C 4. Phosphorus/creatinine ratios in urine were measured in 9 patients on 30 different occasions in 24 hr. specimens and 12 shorter periods. The range in any one patient and at different periods was found to be considerable and more than masked any slight variation in parathyroid activity.

VII D. Magnesium metabolism in various electrolyte disturbances

D I. Serum magnesium tended to vary reciprocally with calcium.

In/

In 3 calcium infusion tests it was slightly decreased, but not in a fourth case with hypoparathyroidism; in the uraemic patients where serum calcium was depressed, magnesium was high. In 10 cases with renal calculi (Hyperparathyroidism) any increase in calcium was too slight to influence the magnesium to any extent.

D 2. Serum magnesium tended to be high in conditions where acidosis was also present, but this was by no means a constant finding, and it probably does not have a great effect on magnesium. Acidosis was present in all the uraemic patients, but magnesium was raised in just over half. In the chronic acidosis of the patients with ureteric transplants, magnesium was normal in two-thirds, but decreased as the acidosis was corrected. Magnesium was also high in one patient with a low plasma potassium and alkalosis.

D 3. There was no definite relationship between magnesium and potassium in the serum. Both were increased in the patients with uraemia (again not invariably), while in 2 out of 4 cases with potassium deficiency and low plasma potassium, magnesium was again high.

D 4. The effect of operation on serum and urine magnesium was investigated in 8 patients. Urine magnesium was decreased the first day post-operatively in all except one case, but serum/

serum magnesium was virtually unchanged. The usual post-operative changes of the other electrolytes were not always present and as conditions were mild, any marked changes in magnesium were not obvious. Its excretion bore no great resemblance to that of either sodium or potassium.

D 5. A few investigations were made of the effect of adrenal hormones on magnesium metabolism apart from the post-operative studies. A.C.T.H. was given to 5 patients, but again some of the typical responses of the other electrolytes were absent, and magnesium excretion was variable; in the two most effective, it was increased in one, decreased in the other, while in the one in whom there was the least apparent response it increased markedly. The lowest daily excretion was in 2 patients with Simmonds' disease, and the highest in one with Cushing's syndrome. Serum magnesium in patients with endocrine disorders was also variable, being high in the one with Cushing's syndrome and also in one with Simmonds' disease. There was a slight increase after giving A.C.T.H. in one patient in whom it was measured.

VII E. Factors affecting blood cell potassium.

E 1. In patients with a low blood cell potassium, plasma potassium was statistically higher than in those with a normal K_c , but the reverse was not significant. Appreciable numbers/

numbers with normal cell potassium had an abnormal plasma potassium, and vice versa, and other factors obviously influenced the distribution of potassium between the cells and plasma.

E 2. In patients with a low blood cell potassium, plasma sodium was statistically lower than in those with a normal K_c , and higher in patients with a high K_c , although hypernatraemia was rare. From this, tonicity of the extracellular fluid was presumed to have a bearing on blood cell potassium levels.

E 3. Plasma bicarbonate was also statistically lower in those with a low K_c , although many with a normal K_c also had a bicarbonate level below normal. Only two patients with alkalemia were examined, and in both these the K_c was above normal.

E 4. In acute acidosis, low cell potassium and high plasma potassium levels were frequently obtained. In chronic acidosis, normal K_c and plasma potassium results were generally found, plasma sodium also being normal. The rate of development of the acidosis thus affected the results.

E 5. Blood cell potassium measurements were found to be an unreliable guide to the state of body potassium. The patients with acute acidosis (usually as a result of renal failure and anuria) had a low K_c but no obvious overall deficiency.

deficiency. In chronic acidosis there was frequently a considerable deficiency (shown by balance experiments) but normal K_e levels. A low K_e in conjunction with a low plasma potassium and acidosis did suggest a considerable deficiency, but K_e returned to normal long before the deficiency was corrected completely. Tissue analysis in one such patient confirmed the potassium deficiency, although K_e was only at the lower limit of normal. In another patient with acute acidosis, high plasma potassium and a similar level of K_e , tissue potassium was normal.

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