STUDIES IN THE EXCRETION OF UREA.

by

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A Thesis submitted for the degree of Doctor of Medicine of the University of Edinburgh.

March, 1932.

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II/

II. CLINICAL:- THE UREA CONCENTRATION RANGE IN DIAGNOSIS, PROGNOSIS AND TREATMENT OF RENAL INEFFICIENCY.

VALUE/

I. HISTOLOGICAL:-

A COMPARATIVE STUDY IN THE MODE OF UREA EXCRETION.

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INTRODUCTORY:

Medicine, for long an Art governed by empiricism, is gradually undergoing transformation to a Science based on observational and experimental fact. Advance in our knowledge of the ancillary sciences has been general and to this we owe the progress that has been made from the practices of mediaeval superstition and 18th century allopathy. To no science does Medicine owe a greater debt than to Physiology. Increase in our knowledge of the physiology of an organ, of its functions and mode of executing them, is immediately followed by advances in our conception of its diseases and their therapeutics. In recent years, for example, the complex actions of the spleen, liver, and endocrine organs have been unravelled; and with a clearer understanding of their physiology, medicine has shown rapid progress. The work of Barcroft (3), Krumbhaar (20), and Tait (61), among others, has established that the spleen is an organ of complex function and is far from being the useless "blood appendage" it was formerly believed to be. The liver has/

has been revealed as an organ of even more multiple functions, and following the work of numerous physiologists, notably Schafer (50), Whipple (67), Mann and his co-workers (31), and Minot and Murphy (38), is now regarded as an essential for almost every vital process within the body. Last century it was thought to have but one function, that of bile production, which is now considered its least important. In the physiology of the endocrine organs the progress is even more striking. Prior to the pioneering work of Schafer and Oliver (52) on the suprarenal these endocrine organs were either disregarded or unknown. The results of these observers led to the realisation that other than nervous forces are in action in the regulation of the body and its activities, and countless workers, none more notable than the "father of endocrinology" (51), have built up a knowledge which has opened for Medicine a field which, thirty years ago, it had not thought to enter.

In dealing with diseases of the kidney, however, Medicine has unfortunately only had partial guidance from the physiologist. The functions of this organ are in general known, but the method it adopts in carrying them out remains to be established. Little advance has been made in this respect since the discoveries of Bowman, and in the absence of precise knowledge/

Fig. 1. Marcello Malpighi (1628-1661).

knowledge of the intimate mechanisms concerned the progress of Medicine in this sphere has not been commensurate with that made in regard to other organs.

HISTORICAL.

EARLY VIEWS ON KIDNEY FUNCTION.

The earliest workers fully realised the excretory power of the kidney and its ability"to cleanse the blood", and surmised variously as to the methods used for this cleansing. Malpighi (30) regarded the corpuscles named after him as "glands in which the urine is elaborated from the blood" and, though he does not specifically state so, would seem to have viewed them as comparable to the other secretory glands of the body. The tubules he regarded as ducts taking origin from the glomeruli. Ruysch (49) attempted to clarify matters by means of injection methods, such as were to be later followed by Bowman, but in the light of present day knowledge, appears to have been wide of the mark when he suggested that the renal arteries became continuous with the tubules and so enabled the blood to pass its waste products to the exterior/

Fig. 2. Sir William Bowman (1816-1892).

exterior. The fault here, however, was not one of observation but one of technique for the rupture of the thin glomerular wall by the pressure of the injection was no doubt responsible for the apparent continuity of blood vessel and tubule.

Opposed to this view of the connection of tubule and glomerulus was that of Huschke (19), who held that the Malpighian capsules were only connected with the blood vessels and were without connection with the "uriniferous ducts". In this contention he was vigorously supported by Müller (39).

THEORIES OF KIDNEY FUNCTION.

Sir WILLIAM BOWMAN.

The first great advance was made by Bowman (5) who in 1842 detailed his experiments, and the observations thereon which led to the establishment of the first acceptable theory of renal function. Working with combined injections of bichromate of potassium and acetate of lead, he was able to demonstrate the dual character of the kidney blood supply, drawing attention to the character of the glomerular supply with its afferent artery, capillary tuft, and efferent artery, and to the second capillary plexus supplied to the tubule from the efferent glomerular vessel. The full value of this work is probably most easily understood by comparing the original plate of Bowman (fig.3)

showing/

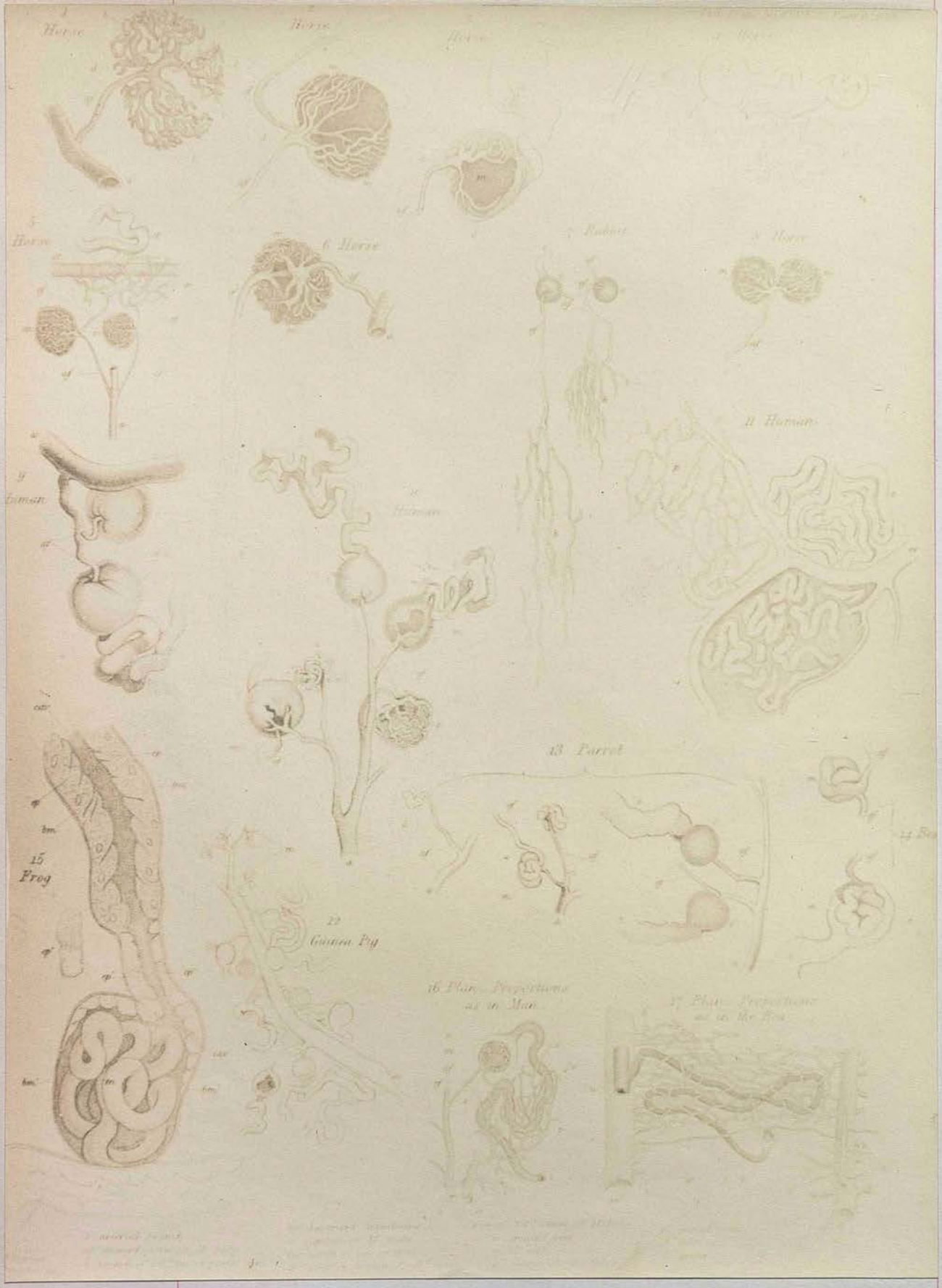


Fig. 3. Plate reproduced from Bowman's communication "On the structure and use of the Malpighian bodies of the kidney", Phil. Trans. Roy. Soc., London, 1842, cxxxii, 78. Shows glomerular structure in man, horse, rabbit, guinea-pig, parrot, frog, and boa.

showing the renal circulation in man and various animals, with that given in any present day text book. Our knowledge of the kidney blood supply has advanced little in the succeeding 90 years. Bowman also drew attention to the delicate membrane which intervened between the blood and the lumen of the Malpighian corpuscle.

> "Reflecting on this remarkable structure of the Malpighian bodies and their singular connection with the tubes I was led to speculate on their use. It occurred to me that as the tubes and their plexus of capillaries were probably..... the parts concerned in the secretion of that portion of the urine to which its characteristic properties are due (the urea, lithic acid, etc.), the Malpighian bodies might be an apparatus destined to separate from the blood the water portion."

> "It may be considered highly probable that the epithelium of the uriniferous tubules is continually giving up its effete particles and undergoing a gradual decay."

It is thus clear that he regarded the glomerular function as that of water filtration from the blood. The urinous principles were supposed to be deposited in more or less solid form in the tubule cells and then these "sparingly soluble" substances had in the glomerulus the "additional and extraneous source of water" for their solution. Briefly then, Bowman's view can be regarded as a combination of a passive filtration of water by the glomerulus and an active secretion of the urinary solids by the tubule cells.

KARL LUDWIG/

Fig. 4. Karl Ludwig (1816-1895).

KARL LUDWIG.

Ludwig (24,25) was unable to accept this view of Bowman', and two years after its appearance he suggested that the kidney function was an entirely passive one. He regarded Bowman's capsule as a passive filter which removed from the blood all the plasma constituents except those retained by the osmotic power of the proteins. This filtrate then passed down the tubule and became converted to urine by the passive absorptive action of the renal tubule cells. From the first Ludwig regarded this theory as one which was open to numerous obvious objections and it is not surprising to find that it was later much amended both personally and in association with others (26).

These first two theories thus accepted the filtrative function of the capsule but differed as regards the nature of the filtrate and the part played by the tubules.

RUDOLPH HEIDENHAIN.

In 1874 Heidenhain (16), while accepting in the main the view of Bowman, stated that the function of the capsule was an active one, not passive as Bowman thought/

Fig. 5. Rudolph Heidenhain (1834-19-) .

thought. Heidenhain thought that the epithelial cells of the capsule were secretory in nature and actively secreted water with a low salt content from the blood of the glomerulus. This then passed down the tubule and received the "solid" secretion of the tubule epithelial cells, this being secreted normally with a small amount of water, but with a much larger amount if diuresis was occurring. This view of function Heidenhain supported experimentally, his chief experiments consisting of the parenteral introduction of dyes, and the observance of the part of the kidney in which these dyes became visible.

"THE MODERN THEORY" AND RECENT MODIFICATIONS.

Following Heidenhain's work the purely physical view of kidney function was completely discredited and the vital theory went unchallenged for many years. Cushny (9) in 1917 suggested that Ludwig's conception of the capsule as a filter, removing from the plasma all except protein, was still tenable, but that Ludwig was wrong in applying a physical explanation to account for concentration. Cushny regarded the capsular filtrate as a fluid containing two types of substances: "threshold and no-threshold substances". The former comprised/

comprised dissolved blood constituents which were of further use to the body and were filtered off by the capsule along with the fluid of the plasma. In passing along the tubule, absorption by the tubule cells led to the concentration of each such substance in the blood being restored to normal levels, and only when this concentration reached a definite height which he called "the renal threshold" for the substance was it allowed to pass out into the urine. The no-threshold substances were filtered off by the capsule along with the threshold bodies but their excretion into the urine occurred without regard to their concentration in the blood, no absorption occurring. It is now suggested that many of the substances regarded by Cushny as no-threshold in type are really threshold substances with low renal threshold values.

In suggesting an active and selective absorptive function for the tubules, Cushny agreed that it might be possible for one part of the tubule to be absorptive while another part was secretory in function, but did not see any need for postulating such a double tubule function in explaining kidney action. Loewi (23), Metzner (37), and Starling and Verney (59) have since suggested/

suggested that the tubules do carry out such a double function. The last workers perfused the isolated kidney with blood from a heart lung preparation at normal pressure before and after poisoning of the tubule cells with cyanide and obtained results suggesting that while water and chloride were glomerular in origin urea was passed into the urine as a result of secretory activity on the part of the tubule epithelium.

White and his co-workers (71,72) have advanced a theory of double function for the glomerulus, suggesting that its activity is of the nature of simultaneous secretion and filtration.

In contrast with these views mention must be made of those of Lamy and Mayer (21), and later Brodie (6). They regarded the glomerular capsule as playing no part in the actual formation of the urine but merely acting as a means of propulsion, its contraction driving the urine along the tubule.

Thus, five main views have been held as regards the kidney's mode of action, varying in respect of nature of action of glomerular capsule and the tubule epithelium. Bowman regarded the capsule action as passive filtration while that of the tubule was active secretion. Ludwig looked upon both glomerular and tubular actions as entirely passive. Heidenhain stated that both capsule and tubule were actively secretory/

secretory. Cushny viewed the capsular function as passive filtration and that of the tubule as active absorption; while Starling and Verney, Loewi, and Metzner postulated a passive filtrative function for the capsule and active secretory power for the tubules. White regards the glomerulus as simultaneously active and passive. Of these theories that of Ludwig is perhaps the only one which is devoid of supporters at the present time.

APPLICATION OF ABOVE THEORIES TO UREA EXCRETION.

Viewing these theories from the aspect of urea excretion it will be seen that the Bowman and Heidenhain theories regard the excretion of urea as tubular; Ludwig and Cushny as glomerular; while Starling and Verney postulate its excretion by both glomerulus and tubule but stress the secretion of it by the tubule cells. Cushny specially mentioned urea as a no-threshold body but found some difficulty in reconciling this view with its different concentration by the kidney to that of the other no-threshold bodies such as creatinine. Oliver (42) follows Cushny in claiming urea/

urea as a no-threshold substance. Rehberg (47), Ekehorn (13), and Mayrs (36) accept Cushny's view of urea elimination except that they regard it as a low threshold body rather than no-threshold, and so overcome the difficulty of its different concentration. Samson Wright (75) regards it as "for all practical purposes a no-threshold body".

INVESTIGATIONS OF UREA ELIMINATION.

TOXIC NEPHRITIS.

With a view to unravelling the mode of excretion of this substance, which is universally regarded of maximum importance in kidney and body activity, much experimental work has been done. Mention has already been made of the work of Starling and Verney (59) following cyanide poisoning of the tubules. Much similar work has also been done following the production of nephritis by poisons, especially oxalates, corrosive sublimate, uranium nitrate, potassium chromate, and cantharidin. In this group falls the work of Schlayer and Hedinger (53), Takayasu (62), Schlayer and Takayasu (54), Pearce (43), Pearce, Hill and Eisenbrey (44), Folin, Kaisner and Denis (14), and Dunn and Jones (12). Opinions vary in this series. Prior to their paper quoted below Marshall and Crane (32) had suggested that urea was secreted by the tubules/

tubules. In this they are supported by the work of White(68,69,70) and Underhill (63); the latter states

> "It is considered that the results of the experiments on the relative concentrations of urea, creatinine and inorganic phosphate are incompatible with the 'filtration reabsorption' hypothesis of kidney function in its present form. It is concluded that the kidneys must actively secrete one or more of these substances into the urine".

Objections which seem justifiable have been raised to these methods from very numerous sources. It certainly seems that no true indication of normal kidney function can be arrived at by studying that function in a kidney which has been rendered abnormal. In Starling and Verney's series of experiments the result seems to be entirely dependent upon the glomerular capsule preserving its integrity under the poison. The appearance of protein in the urine which was noted a short time after the commencement of the experiment suggests that such integrity is not maintained. If the capsule is permeable to colloids, soluble substances can certainly pass through it.

UREA EXTRACTION METHODS.

Attempts have been made chemically to compare the amounts of urea which can be extracted from the kidney with the amounts which are passed in the urine. Such work, carried out by Marshall and Crane (33) who found less/

less urea in renal extracts than in urine, seems to indicate that concentration of urea intracellularly does not occur in the mammalian kidney at least, though some of the results would seem to suggest such an occurrence in the frog kidney. Similar previous work by Marshall and Davis (34) on the dog, and Cushny (8) and Mayrs (36) on the rabbit support this view. Leschke (22), however, suggests that localised concentration of urea does occur in the cells of the convoluted tubules. Experiments along these lines are, however, necessarily inconclusive, for, as Starling and Verney point out, it is quite possible for tubular secretion to occur without previous concentration in the cells.

The work of Nussbaum (40,41) suggests that urea is secreted by the tubule epithelium. His experiments are too well known to require detailing.

RATE OF UREA ELIMINATION.

Observations on the rate of urea elimination have also been used as evidence in favour of either urea secretion or filtration. Ambard (1) suggested his constant governing this elimination and this has since been frequently amended by F.C. McLean (29), Widal and Javal (73), Walker and Rowe (64), and others. The results obtaining therefrom have been limited and

their/

their interpretation has, as in those obtained by other methods, been varied. Drury (11) working with the rabbit along similar lines concluded that

> "the rate of urea excretion continues to rise in direct proportion to the increase in blood urea concentration",

and would seem to support the glomerular filtration of urea.

MICRO-DISSECTION METHODS.

Though recent, the work of Wearn and Richards (66) is already well known. These investigators employed microdissection methods to obtain samples of glomerular filtrate. The possibility of blood contamination was excluded by the absence of albumin. The presence of urea, chloride and glucose in the protein-free filtrate offered strong evidence of the filtration of these substances by the glomerular capsule. Similar work has been carried out by numerous investigators, notably White and Schmitt (71, 72) and Ekehorn (13).

HISTOLOGICAL INVESTIGATIONS.

Histological study would seem to offer a way of clearing up the problem and numerous methods have been devised towards this end.

Herring (17), using the elasmobranch kidney, showed secretion droplets to come from the cells of the tubules. It has since been suggested that these contained urea. As noted later, however, the elasmobranch kidney is not comparable with that of the mammal, and such a tubule secretion may be attributable to a difference in function.

Leschke/

Leschke (22), and later Oliver (42), obtained precipitation of urea by mercuric nitrate and by this means showed urea in the cells of the convoluted tubules, both suggesting its secretion by this part of the tubule. The method is fully criticised by Oliver (42) in a later paper where he replaces the mercuric nitrate with the xanthhydrol precipitation method.

XANTHHYDROL AS UREA PRECIPITANT.

Xanthhydrol as a precipitant for urea was first suggested by Fosse (15) and numerous workers have since used his method with varying results. Policard (46) found no urea present in the tubule cells but much in the glomerular capsules and lumina of the tubules and concluded that free urea is non-existent in the kidney cells, but suggested that it might be present combined in the protoplasm of these cells. Chevalier and Chabanier (7) demonstrated the crystals in the cells of the convoluted tubules, within the blood vessels, and in the lumina of the ducts of Bellini. Stübel(60) using the same method reported the crystals as present in the cells of the convoluted tubules, within Bowman's capsule between the capillaries, in the lumina of the straight tubules, in the tissue between the convoluted tubules/

tubules and within the blood vessels. Oliver (42) showed crystals present in similar situations to those reported by Stübel and suggested from his results that

> "the urea passes through the glomerular capsule in the same concentration as that found in the plasma. A certain amount is added to this filtrate by excretion through the cells of the proximal convoluted tubules, and the ultimate concentration is reached by an absorption of water in the remainder of the tubule".

He considers that this does not affect the fundamentals of the "modern theory", as Cushny suggested that an active secretion in the tubules might be necessary to supplement "the modern view". Piras (45), Walter(65), and Hollman (18) all report much similar observations. In the work of Oliver, Piras, and Walter, the liver was used as a control organ, Oliver and Piras finding urea present in the blood vessels only, whereas Walter reported on its presence both in the blood vessels and in the hepatic cells. In all of the above-mentioned experiments the xanthhydrol precipitant was much similar in nature and the technique employed varied only in small details.

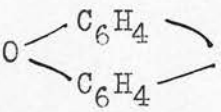
In the above workers' experiments the animals used were comparatively limited. Stübel, Oliver, and Walter used only rats; Policard, rabbits; Chevalier and Chabanier, cat, dog, and guinea-pig; and Piras, rabbit, guinea-pig, rat and dogs.

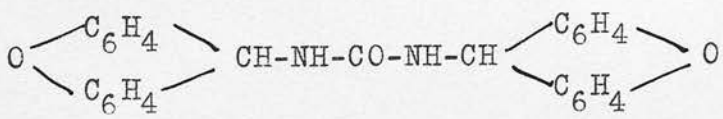
AIM OF PRESENT SERIES OF EXPERIMENTS.

In the present series of experiments a comparative study of the excretion of urea has been attempted. Use was first made of the kidneys of elasmobranch fishes (dogfish and skate), this part of the study embracing four distinct series of experiments. Following these experiments, the kidneys of frogs, mice, rats, guinea-pigs, rabbits, cats, dogs, one monkey, and man were utilised. The range of material was thus a wide one.

In view of the criticisms of Oliver (42) following upon his use of the method, mercuric nitrate was discarded as a urea precipitant; and xanthhydrol has been used exclusively throughout.

METHOD EMPLOYED.

Xanthhydrol  is insoluble in water but soluble up to 6% in glacial acetic acid. When brought into contact with urea the insoluble compound, dixanthylurea,



results. This compound is insoluble in water and in glacial/

Fig. 6. Crystals of dixanthyl urea.

glacial acetic acid. It is crystalline in character, the crystals being acinar in type as shown in fig. 6 . Thus when any organ is treated with this precipitant the urea is converted to dixanthylurea and fixed in the situation which it occupied.

The xanthhydrol used was obtained from Poulenc Frères of Paris. Other specimens were used prior to this but were found much less satisfactory. No attempt was made to prepare the xanthhydrol personally as suggested by Stübel and Oliver. Two grams of xanthhydrol were triturated with 10-15 ccs. of methyl alcohol and 20 ccs. of glacial acetic acid were then added. This method of preparing the precipitant fixative was similar to that adopted by Oliver.

Two methods of fixation were used in the series. In the majority the kidneys were removed immediately the animal was killed and pieces placed in the xanthhydrol solution for 8 to 12 hours. In order to check the results obtained by this method a minority of the animals were anaesthetised, and xanthhydrol, in amount varying with the animal, was injected into either the abdominal aorta high up or into the renal artery. The animal was then killed, kidneys immediately removed and placed in the xanthhydrol solution for 6 hours.

After this urea fixation the pieces of kidney were placed in absolute alcohol for 48 hours, four changes/

changes of alcohol being used over this period. Following transfer to xylol for two hours, they were embedded in paraffin. The paraffin sections, cut at 4-5 μ, were lightly stained with Delafield's haematoxylin only, counterstaining with acid stains being found to obscure the crystals.

EXCRETION OF UREA.

IN ELASMOBRANCH KIDNEY.

In the elasmobranchs urea plays a much more important part than it does in the mammal. In the latter it serves merely as a means of excretion of nitrogenous waste, but in the elasmobranch a further purpose is undoubtedly served by the large amount which is present in the blood. "The extraordinary concentration of urea" in the serum of elasmobranchs has been commented upon by many observers. Staedeler and Frerichs in 1858 (*58*) pointed out the "colossale Quantitaten" and since then von Schroeder (*55*), Bottazzi (*4*), Rodier (*48*), Dakin (*10*), Winterstein(*74*), Macallum (*27,28*), and Smith (*57*) have noted it and arrived at various conclusions as to the part it plays. The amounts stated to be present in the blood vary within small limits in these authors' works, but a general figure seems to lie between the 1.8% given by Winterstein/

Winterstein and the 2.02% given by Macallum, as compared with the 0.02% present in the serum of man. Von Schroeder estimates the whole blood content as 2.6% and suggests the serum must contain 3.1%. Macallum regards this large amount in the blood as an indication of "how relatively inert in their elimination are the kidneys of these fish". This suggestion, however, seems hardly likely to be the correct one and most of the other authors agree that the part played by urea is to regulate the osmotic tension of the blood, a view concurred in by Macallum in a later paper (28), in which he shows the osmotic tension in the serum of the dogfish to be -2.035° C (as indicated by Δ), while the total salts of the same give a Δ of -1.073° C, the difference being due to urea. Dakin showed that the osmotic tension of the blood fell when the fish was transferred from sea water to fresh water, death resulting after some hours from cardiac exhaustion. He concluded that

> "urea is present not only to bring the osmotic tension up to that of sea water but as a necessary constituent of the blood without which the regular beating of the heart is impossible".

Bottazzi demonstrated that the osmotic tension of the blood varies as that of the sea water and that there was despite this much less chloride in the blood than in sea water. Rodier, commenting on this from his own/

own results, suggested that urea makes up the difference in osmotic tension between the blood and sea water. Smith, while failing to confirm Macallum's figures for the NH_3 content confirms those for urea and regards urea as a metabolite specifically retained for osmotic purposes.

Babkin and Komarov (2) have reported that "urea in concentration of about 1% is excreted with the gastric juice of the Raja diaphanes". It may be that this secretion is employed as a secondary means of eliminating urea from the blood and of assisting in the maintenance of blood osmotic tension. It is of interest in this connection to comment upon the work of Martin (35) who reports a series of experiments on the nitrogen content of gastric juice of man and notes the presence of all the nitrogenous constituents of urine.

METHODS EMPLOYED.

In view of this high urea concentration in the serum of these fish, dogfish and skate were first used in this study. Three fish (2 dogfish and 1 skate) were killed immediately on removal from sea water by pithing the brain and spinal cord. The kidneys and pieces of liver were quickly removed and placed in xanthhydrol/

xanthhydrol solution. This first group was intended merely as controls for the further groups.

The second group consisting of 6 dogfish and 1 skate were injected intraperitoneally with 2-5 ccs. of a 5% solution of urea and then returned to sea water. The injection was given to ensure a supply of urea for elimination, it being thought that the return to sea water might necessitate the retention of serum urea for osmotic purposes. The fish were killed (as before) at intervals varying from 10 to 60 minutes and the kidneys removed and placed in xanthhydrol solution.

In the third group advantage was taken of the part played by urea in the regulation of the osmotic tension of the blood of these fish. Only dogfish were included in this group, five being used. The fish were placed singly in 2 gallons of sea water in a small tank for 15 minutes following which tap water was added. The first fish of this group was killed 15 minutes after the addition of 1 gallon of tap water. The others were killed after additions of 1 gallon each 15 minutes, at intervals of 30, 45, 60 and 90 minutes. By this method it was anticipated that a full urea excretion would be obtained to balance blood osmotic tension with the reduced tension of the diluted sea water.

This/

This method was further extended in the fourth group which embraced 2 dogfish. These were placed as before in 2 gallons of sea water following which dilution was carried out by 1 gallon additions of tap water each 15 minutes until death occurred. With the first additions the dogfish remained active and apparently normal, but exhaustion soon became evident and death resulted 135 and 115 minutes respectively after the commencement of the experiment. As before, the kidneys and pieces of liver were immediately removed.

DISCUSSION OF RESULTS.

The results obtained showed certain variations in the four groups. All of them gave abundant evidence of glomerular excretion, but the part played by the tubule cells appeared to vary with the demands placed upon the kidney.

The first group gave probably the most important results and consequently it is unfortunate that it embraced only 3 fish. It was, however, intended to use this group only as controls for the further experiments, and no opportunity has presented itself of extending the group since the examination of the sections has been completed. In all three fish abundant crystals were found in the glomerular capsule, in/

Fig. 7 . Dogfish. Removed from sea water and killed. Section of kidney shows crystals in lumina of tubules. Tubule cells devoid of crystals. (x 260).

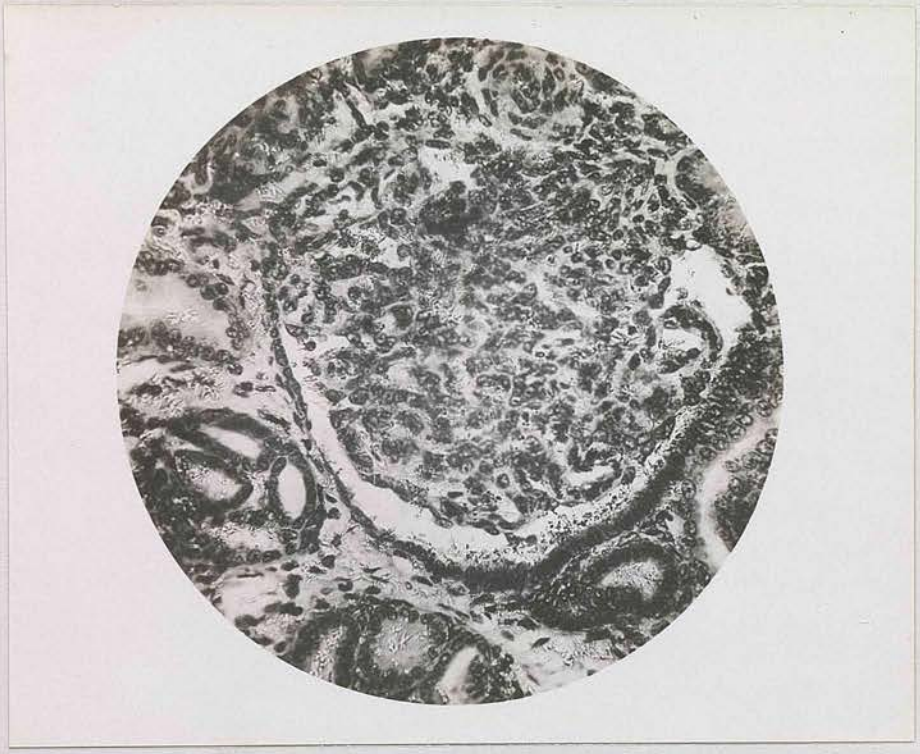


Fig. 8. Dogfish. As in fig. 7. Shows crystals in glomerular capsule, interstitial tissue and lumina of tubules. (x 260).

in the lumina of the tubules, in the interstitial tissue, and in blood vessels. In none of the sections examined were crystals seen within the cells of tubules. Fig. 8 illustrates the characteristic glomerular findings, while fig. 7 shows the crystals within the tubule lumina while the cells are devoid of crystals.

The results obtained in the remaining groups were similar, crystals being found in blood vessels, interstitial tissue, glomerular capsules, and tubular lumina as in the first group, while in addition crystals were seen within the cells of many of the tubules. The number of crystals within the cells varied in the different groups and in different members of the groups. In the injected fish the crystals were very abundant in all parts, those within the tubule epithelium being present in all parts of the cells. Those killed following dilution of the sea water showed exactly similar situations of the crystals, but it was observed that the number of crystals diminished somewhat as the dilution increased. In the sections obtained from the fish which were allowed to die following increasing dilutions of the sea water, the findings approached much more to those obtained in the first group, but here too crystals were present within the tubule cells. The crystals were everywhere scantier/

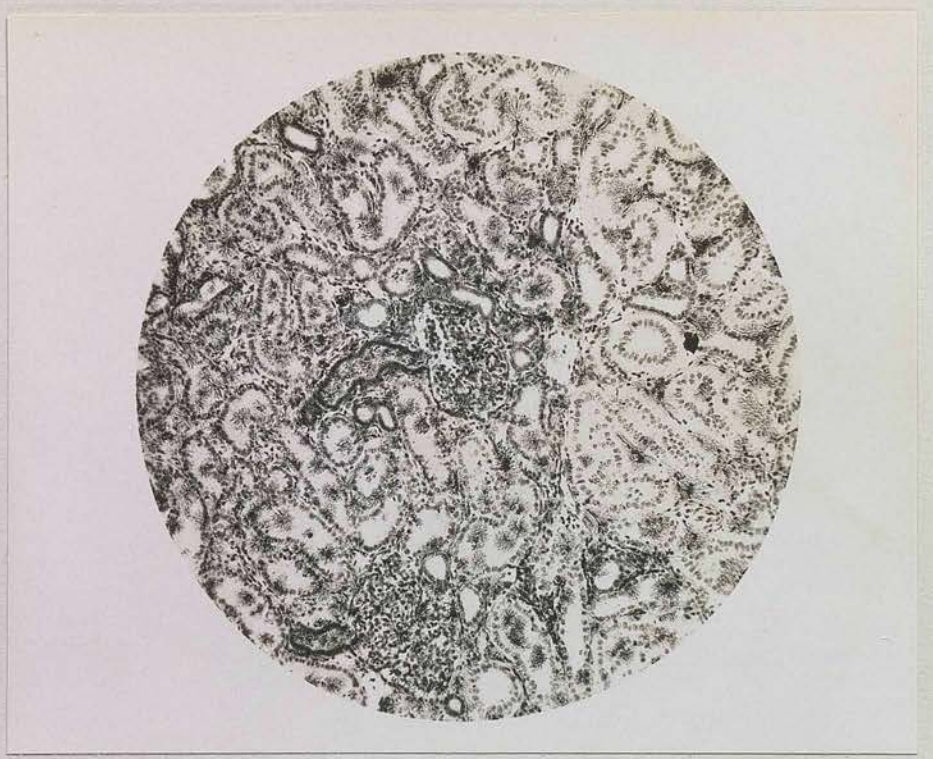


Fig. 9. Dogfish. 3 ccs. 5% urea injected intraperitoneally. Killed 45 mins. later. Section of kidney shows crystals in glomerular capsule, tubule lumina and interstitial tissue. (x 90)

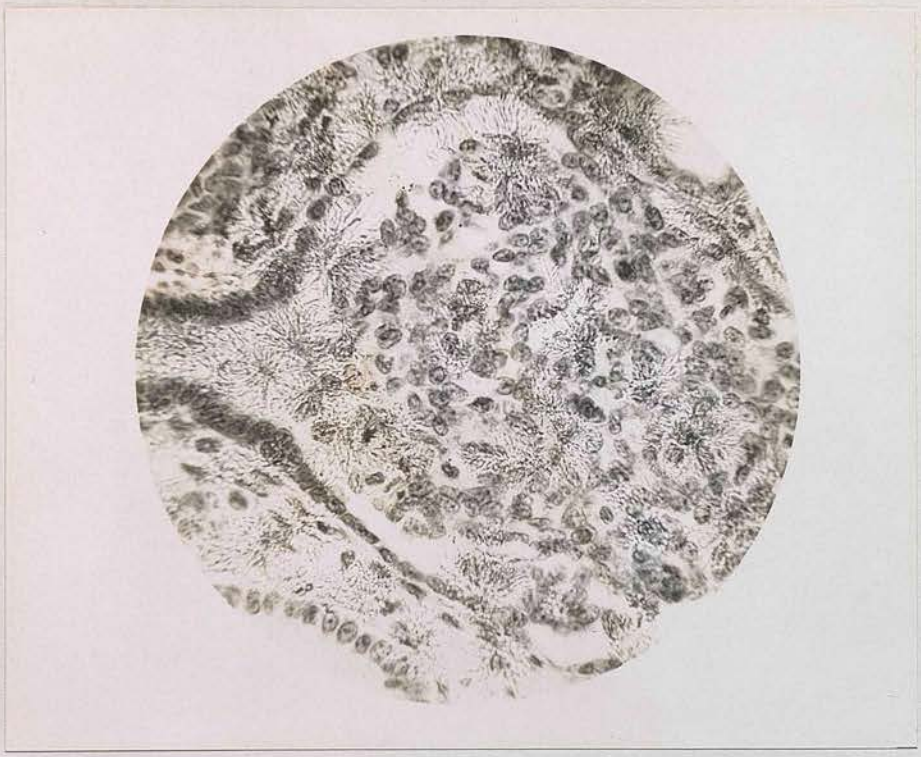


Fig. 10. As fig. 9. Shows crystals in glomerular capsule and interstitial tissue. (x 435)

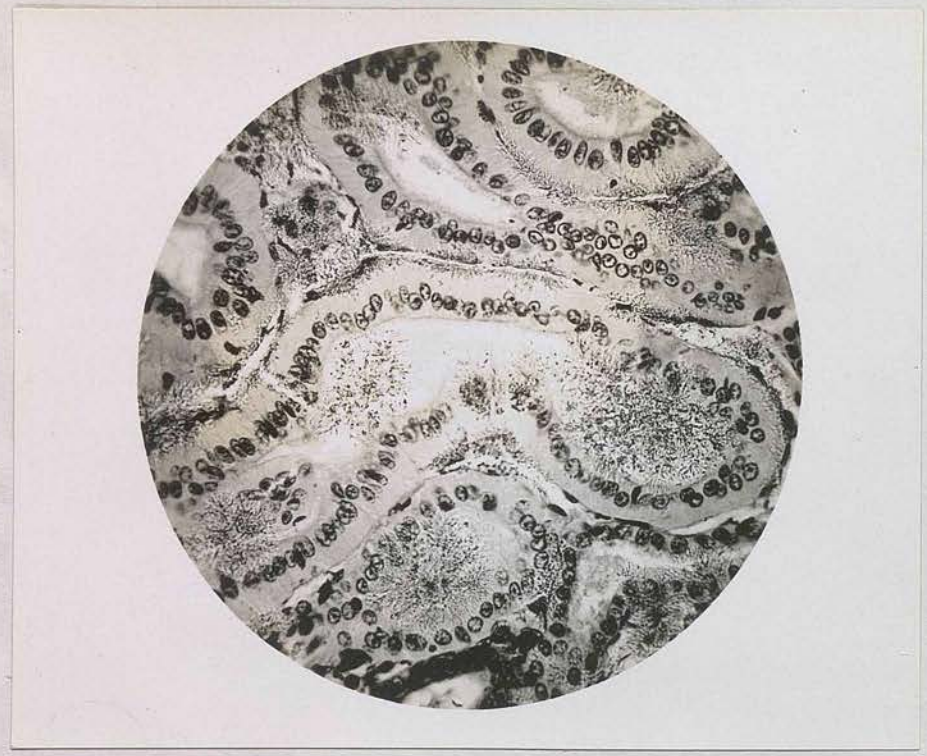


Fig. 11. Dogfish injected with 2.5 ccs. 5% urea intraperitoneally. Killed after 40 mins. Section of kidney shows crystals in cells and lumina of tubules. (x 260).

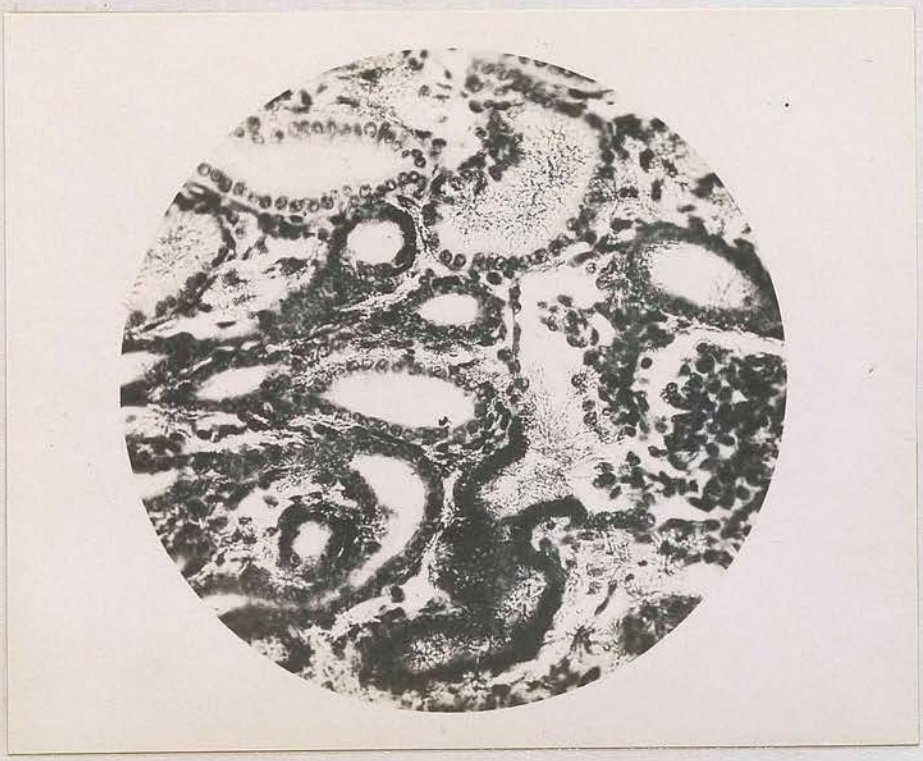


Fig. 12. As fig. 11. Shows crystals in glomerular capsule and passing into origin of tubule. Also present in other tubule lumina. (x260).

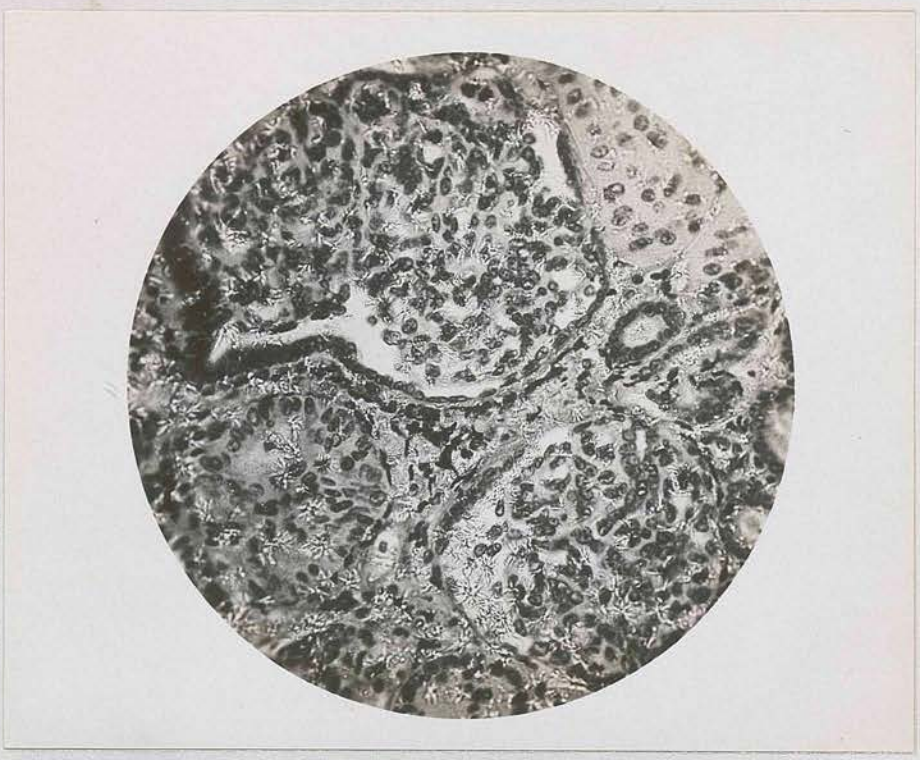


Fig. 13. Dogfish. 2 gallons sea water diluted with 2 gallons tap water (1 gallon at 15-minute intervals). Killed after 30 minutes. (X 260)

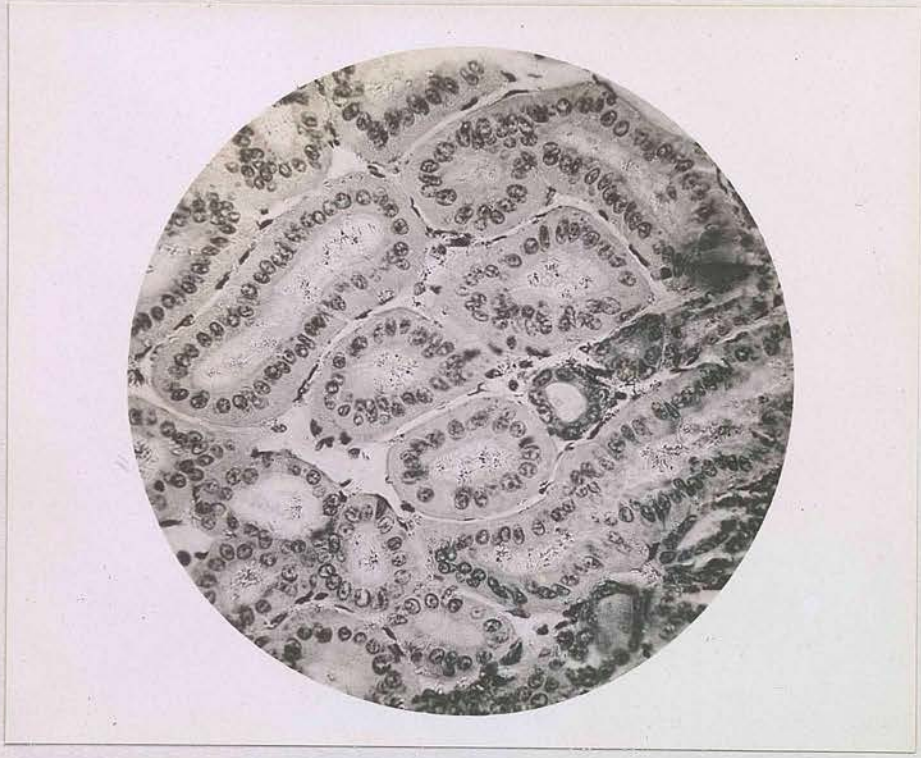


Fig. 14 . As fig. 13 . Death following successive dilutions of sea water. Kidney tubules show crystals in lumina and few crystals in cells. (x 260).

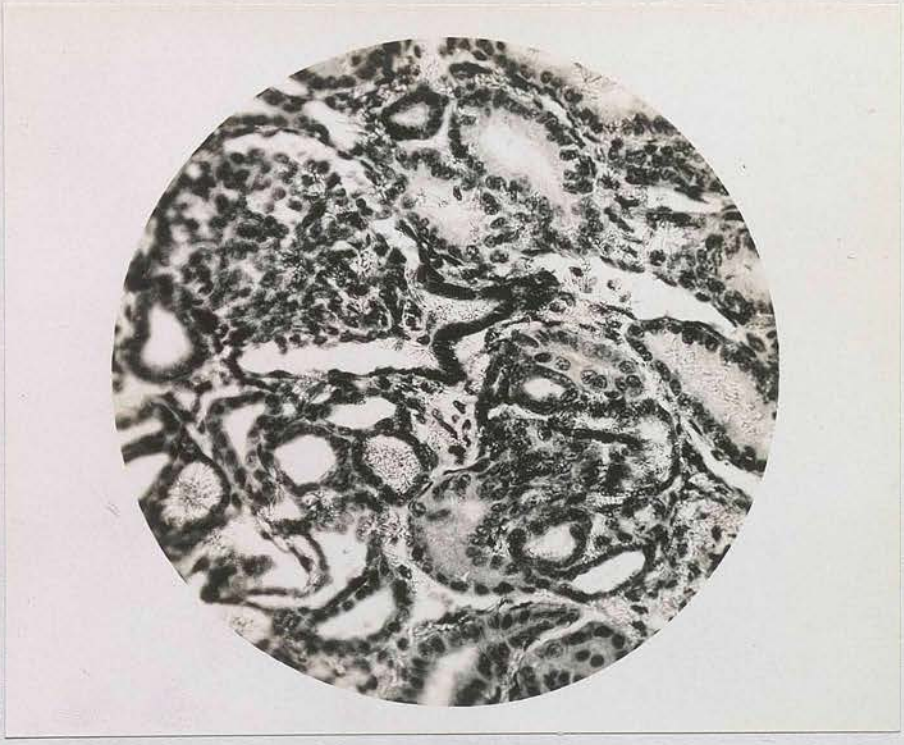


Fig. 15 . Dogfish 15. 2 gallons sea water diluted with 7 gallons tap water each 15 minutes. Death occurred 115 minutes after commencement of experiment. Section of kidney shows crystals in glomerular capsule, tubule lumina interstitial tissue. (x260).

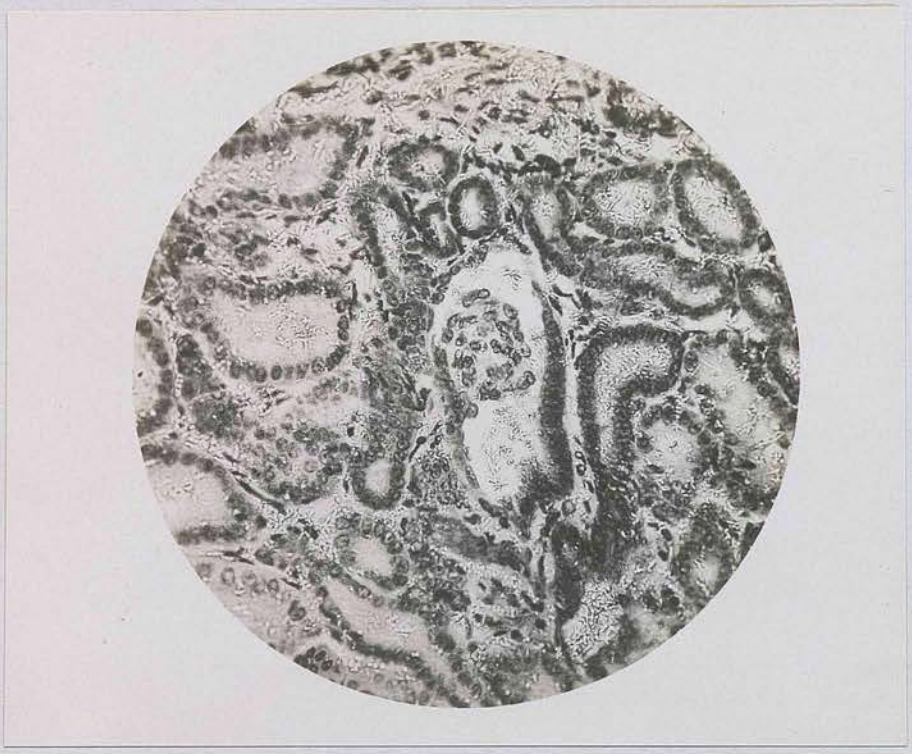


Fig. 16. Dogfish. As fig. 15. Crystals present in glomerular capsule and origin of tubule therefrom. (x 260).

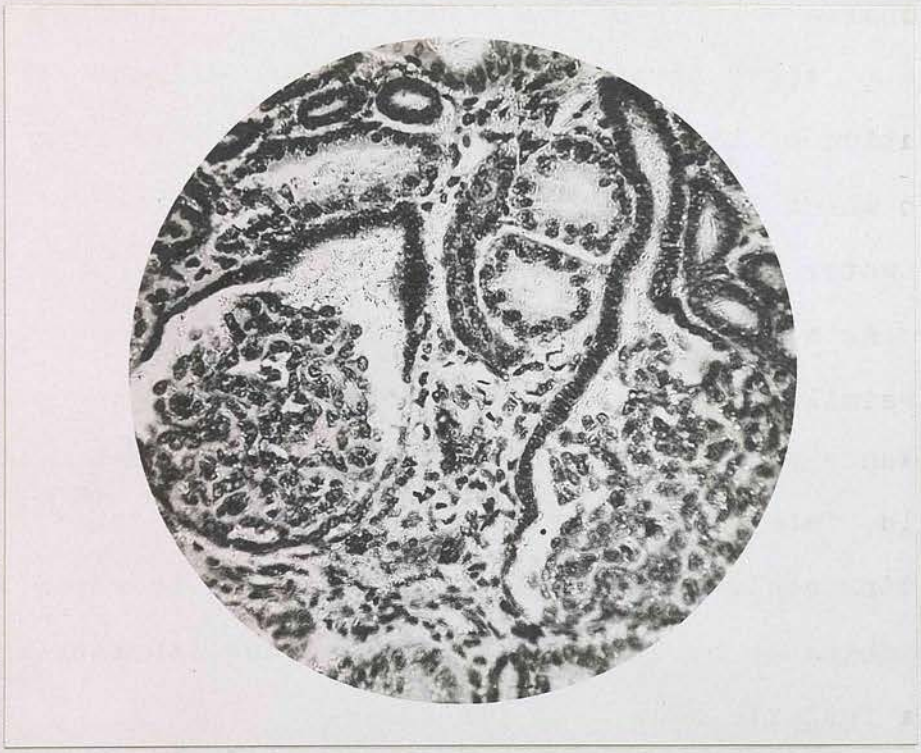


Fig. 17. As fig. 15. Crystals present in glomerular capsule and origin of tubule therefrom. (x 260).

scantier, and those within the cells were mainly confined to the part away from the lumen. Figs. 9-12 ~~is~~ are characteristic of the findings in the injected fish; figs. 13, 14, shows those obtained in a fish killed following dilution of the sea water; while figs. 15, 16, 17 is from the fish which died 115 minutes after the dilution of the sea water was commenced.

As a control pieces of liver were removed from all and similarly treated. They showed in all groups the presence of the characteristic crystals in hepatic cells, intercellular spaces and blood vessels. This finding conforms with the view expressed by van Slyke and White (56) that the liver of the dogfish secretes urea into the bile from its cells.

The results obtained here suggest that the mode of action of the kidney in the elasmobranch varies according to the need for urea elimination. When the excretion is a normal one, as was the case in the first group, it would seem that the elimination is entirely glomerular in character. When, however, an urgent and heavy demand is made upon kidney function the glomerular excretion appears to be aided by a tubular secretion. Such assistance is called for whenever great osmotic imbalance between blood and sea water is present whether resulting from raising of the blood osmotic/

osmotic tension as by injection of urea, or from lowering of the sea water osmotic tension by dilution. The lessened imbalance in the fourth group at death would appear to be the explanation of the scanty crystals in the tubule cells of these.

It cannot be suggested here that the presence of crystals in the tubule cells may result from absorption of urea from the lumen by the cells. The need for elimination and balancing of osmotic tension is so great that absorption after excretion is inconceivable. It thus seems apparent that in these fish the function of at least some tubule cells is secretory and that this secretory activity is called into being whenever the excretory power of the glomeruli is incapable of meeting the heavy and urgent demands placed upon it. If the intracellular crystals had been fewest in those fish where the excretory necessity was greatest, it might have been suggested that absorption was occurring to counteract a slightly excessive excretion and prevent too great a fall in osmotic tension of the blood. The presence of most crystals in the tubule cells of the fish with the most urgent needs for excretion and the fewest in those of the fish with the least needs would/

would appear to render such a suggestion untenable.

IN FROG KIDNEY.

It was realised that the high urea concentration of dogfish blood might be a disadvantage in such a study and might lead to erroneous impressions if similar activity was taken to occur in other animals. Consequently the study was next carried to animals in which the blood urea concentration was much less. Of these the first used was the frog, this being chosen in view of the open character of the frog kidney structure. The double nature of the blood supply to the frog kidney, by renal artery and renal portal vein, was not regarded as rendering it unsuitable.

Injection methods only were utilisable here, each frog being given 1 cc. of a 5% solution of urea into the dorsal lymph sac. At intervals of 20-60 minutes after injection the frogs were killed by pithing of brain and spinal cord, following which the kidneys were immediately removed and placed whole in the xanthhydrol solution. Pieces of liver were also removed as controls.

The crystals seen im the frog kidney were much smaller than those found in the sections obtained from the elasmobranchs and the animals which were later used. The interstitial tissue was everywhere crowded with/

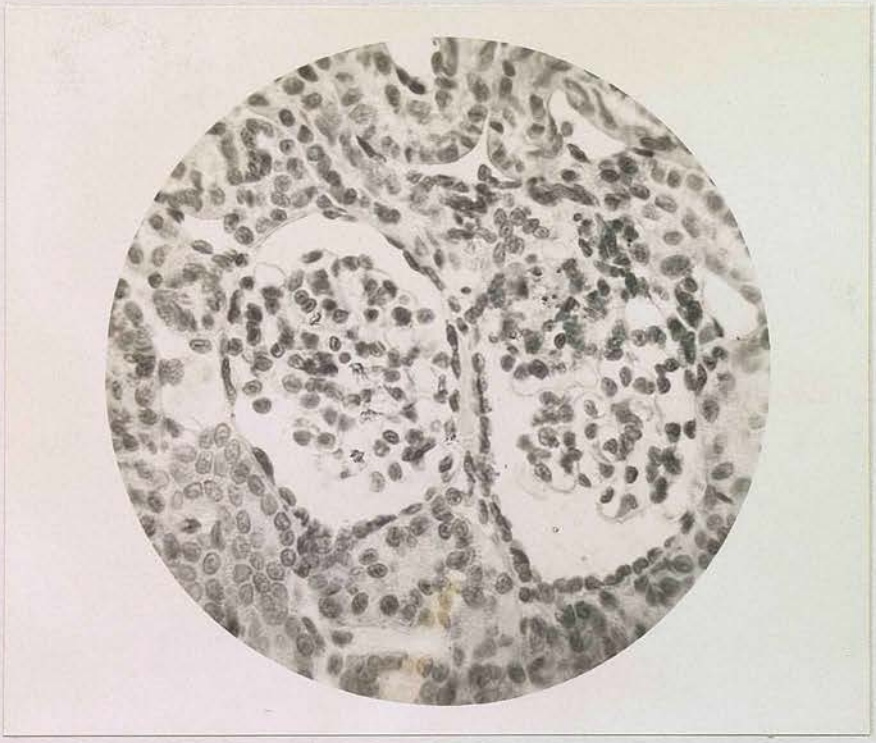


Fig. 18. Frog. Injected with 1 cc. 5% urea into dorsal lymph sac. Small crystals present in glomerular capsules of kidney (× 340).

with them; the capsule of most of the glomeruli and the lumina of the tubules contained them; but no crystals were found within the cells of the tubular epithelium. Fig. 18 illustrates the position of the crystals in the kidney of a frog killed 40 minutes after injection.

IN RAT AND MOUSE KIDNEY.

As it was the animal used in the experiments of Stübel, Oliver and Piras, the rat was next employed. Two groups were used, the first for experiments by injection, the second for experiments by feeding. In the first group 2 ccs. of a 5% solution of urea were given subcutaneously, the animals being killed at intervals varying from 30-90 minutes after injection. The second group were given urea along with their food, 1-2 grams of urea being added to their daily diet, details of which are given below.* This feeding was continued over periods varying from 3-7 days.

Along with this series a number of mice were used. These also were divided into two groups, the injection group receiving 1-2 ccs. of 5% solution of urea, while the feeding group received .75-1 gram of urea daily in their/

*Indian corn 76 grams
Wheat gluten 20 grams
Calcium carbonate 3 grams
Sodium chloride 1 gram
Milk 150 ccs.
The above formed sufficient for 4 rats.

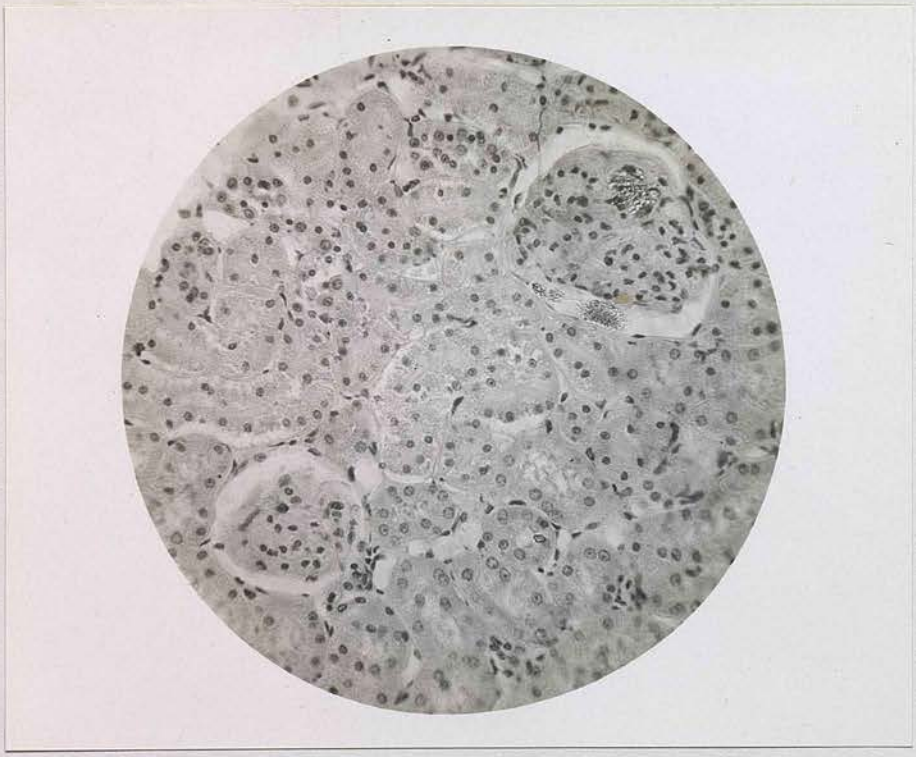


Fig. 19 . Rat. 1 gram urea added daily to diet. Killed after 7 days. Section of kidney shows crystals within glomerular capsule. (x 260).

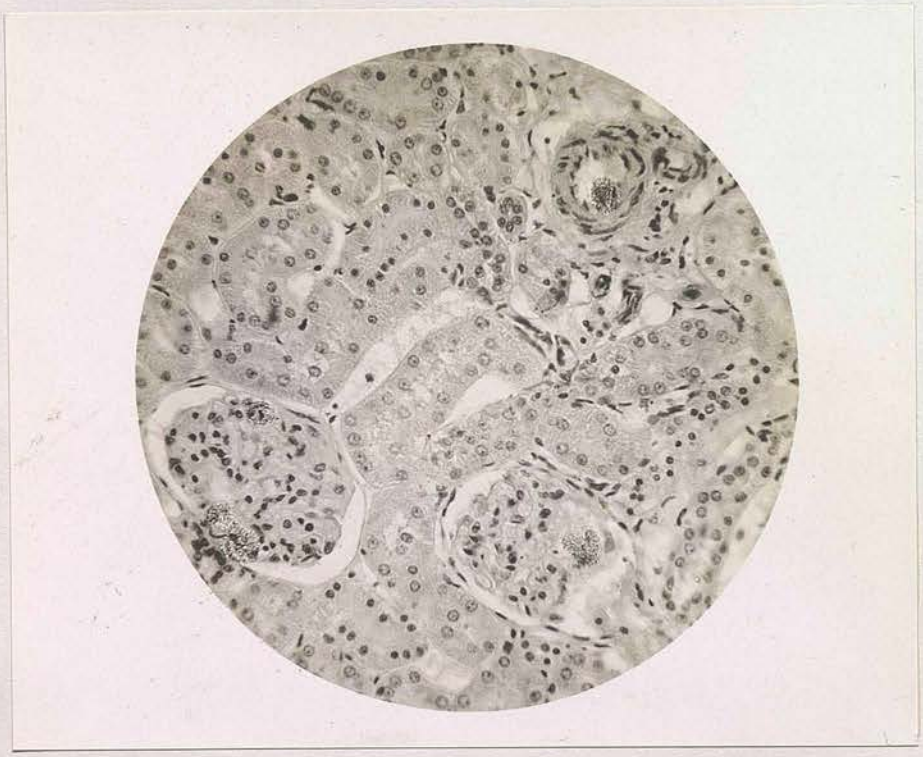


Fig. 20. Rat. 2 grams urea added daily to diet. Killed after 5 days. Section of kidney shows crystals in blood vessel and glomerular capsules. (x 260).

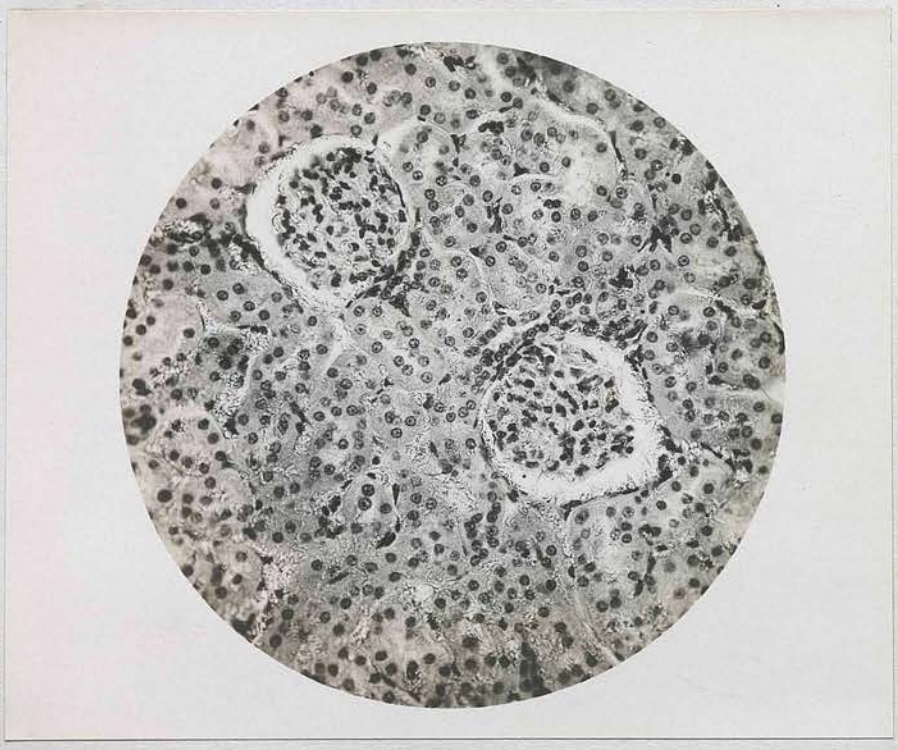


Fig. 21 . Rat. Injected with 1.5 ccs. 5% urea. Killed 45 minutes later. Section of kidney shows crystals in glomerular capsule and interstitial tissue. Crystals in tubule lumina but none within tubule epithelium cells. (x 260)

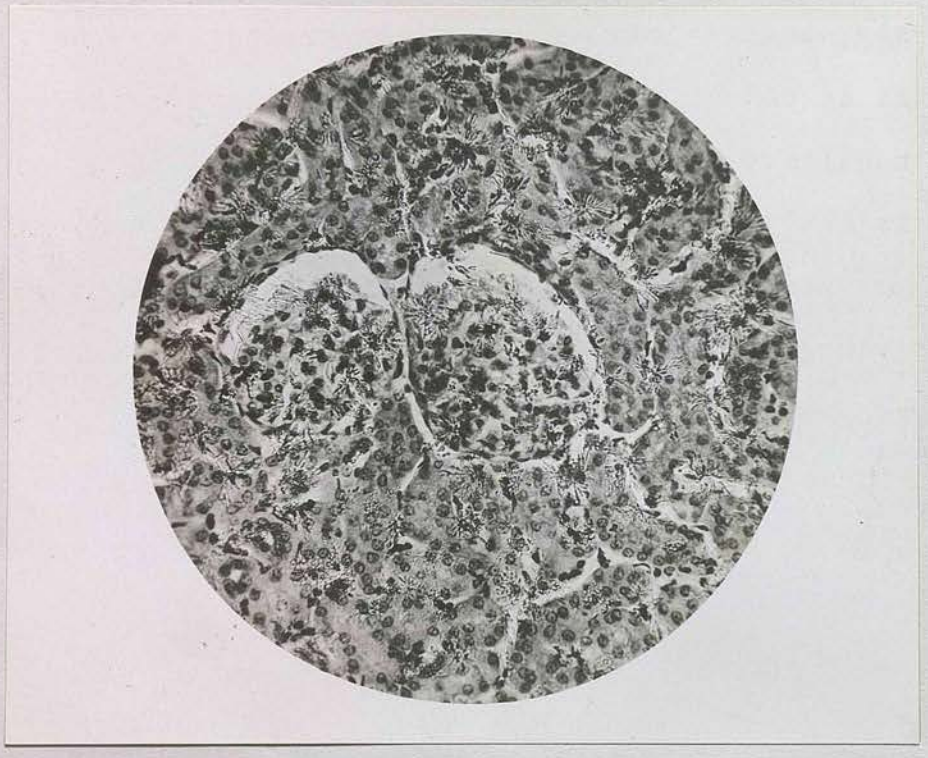


Fig. 22. Rat. Injected with 2 ccs. 5% urea. Killed 60 minutes later. Section of kidney shows crystals in glomerular capsules and interstitial tissue. (x 260).

their customary bread and milk diet. The intervals elapsing before they were killed was as for the rats.

The results obtained were similar in both groups of rats and mice. Crystals were observed in blood vessels, interstitial tissue, glomerular capsules and lumina of tubules, but none were seen in the cells of the tubular epithelium. Of the two methods employed the injection method proved the less successful, too many crystals being found in the kidney sections of this group. Despite the abundance of these crystals, however, none were in the tubule cells.

Three figures illustrate the situation of the crystals in this series. Figs. 19 and 20 show them present in a blood vessel, interstitial tissue and glomerular capsules of fed rats, the tubule cells being everywhere free. Figs. 21, 22 shows the much more numerous crystals in an injected rat kidney, the situation of the crystals being similar.

IN GUINEA-PIG KIDNEY.

In the experiments employing guinea-pigs the methods utilised were much similar to those used for rats. In one group 2-3 ccs. of 5% solution of urea were injected beneath the skin, the animals being killed/

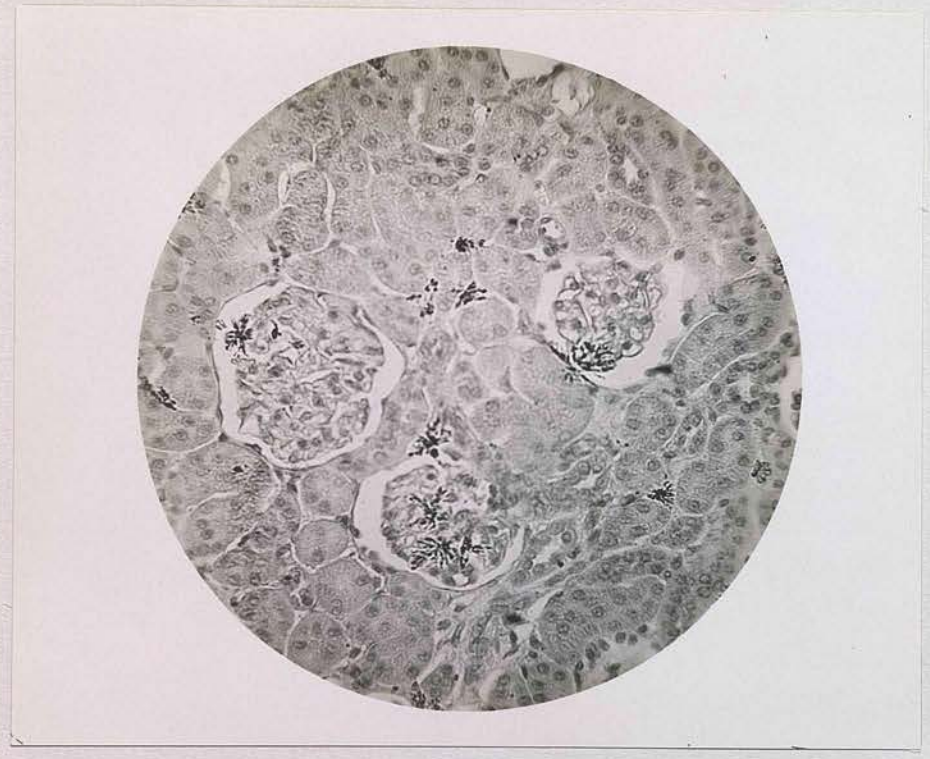


Fig. 23. Rabbit. Injected with 5 ccs. 5% urea. Killed 30 mins. later. Section of kidney (x 260) shows crystals in glomerular capsules and interstitial tissue. No crystals seen in tubule lumina.

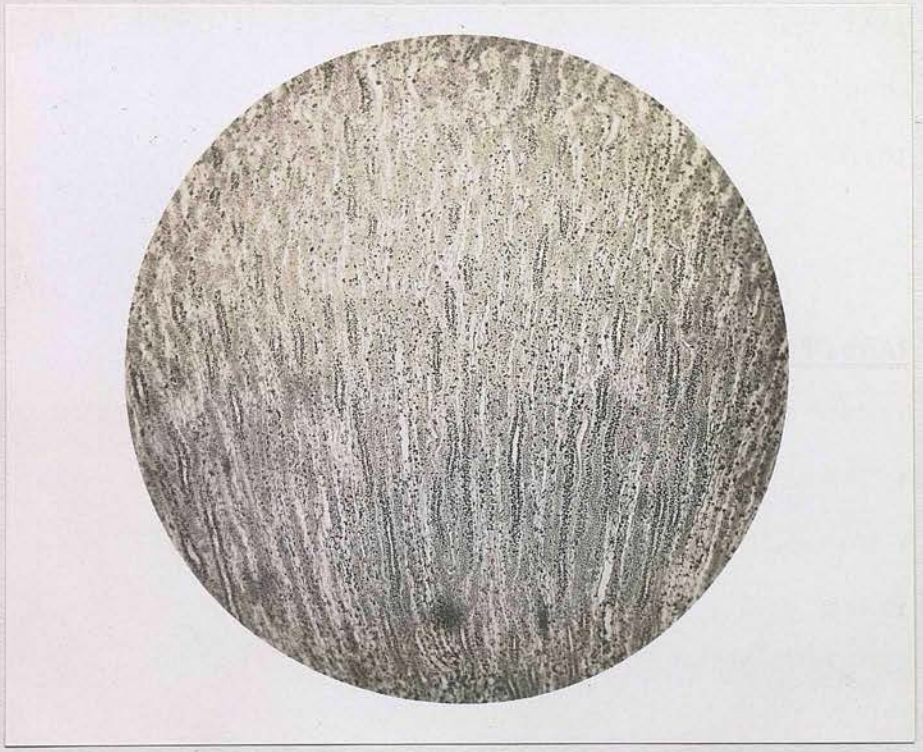


Fig. 24. Rabbit. As fig. 23. Shows dixanthyl urea crystals in lumina of collecting tubules. (x 56)

killed 30-60 minutes later. In the feeding experiments embracing the second group, 1 gram of urea was added to the regular daily diet of "bran mash". In both of these groups the crystals were exactly comparable in site with those found in the rat and mice kidneys.

IN RABBIT KIDNEY.

Use was made of the rabbit kidney following the same two types of experiment. To the first group urea was administered subcutaneously, 5 ccs. of a 5% solution being given, while the second group had 1-3 grams of urea added daily to their regular diet. The intervals allowed to elapse before killing were the same as for the rats.

In the rat experiments the results following feeding were much better than those following injection due to the presence of over-abundant crystals in the latter. With the rabbit the same difficulty was not experienced, the findings in both groups being much similar. The crystals were found in the same situations as in the rat kidney sections, as can be seen by reference to the microphotographs in figs. 23 & 24 The first of these figures is an example of the results obtained/

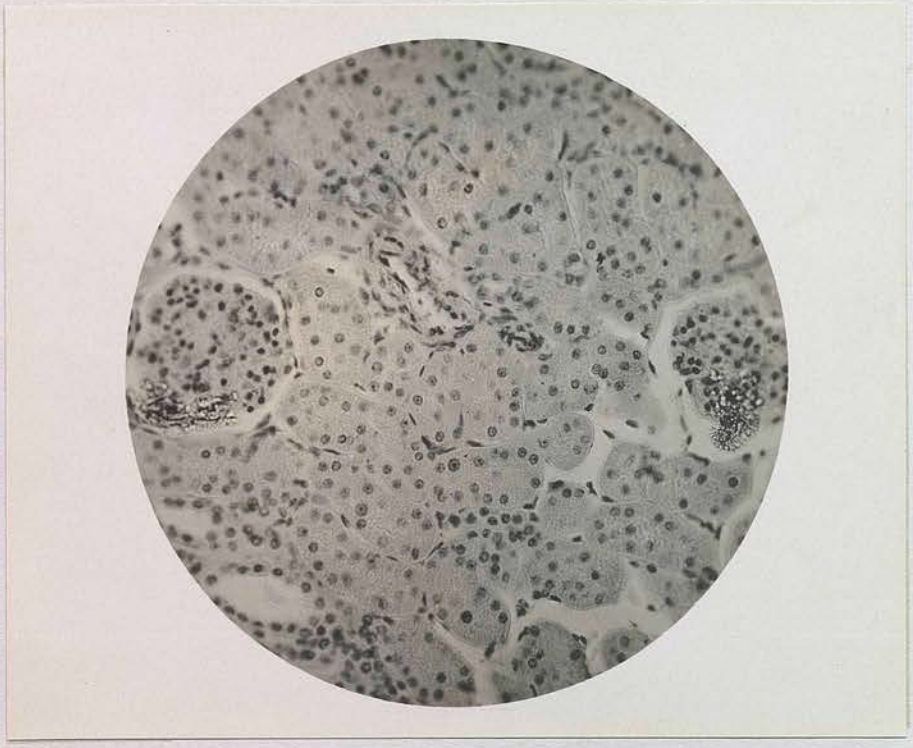


Fig. 25. Rabbit. 1 gram urea added to diet for 7 days. Section of kidney (x260) shows urea in capsules but none present in tubules.

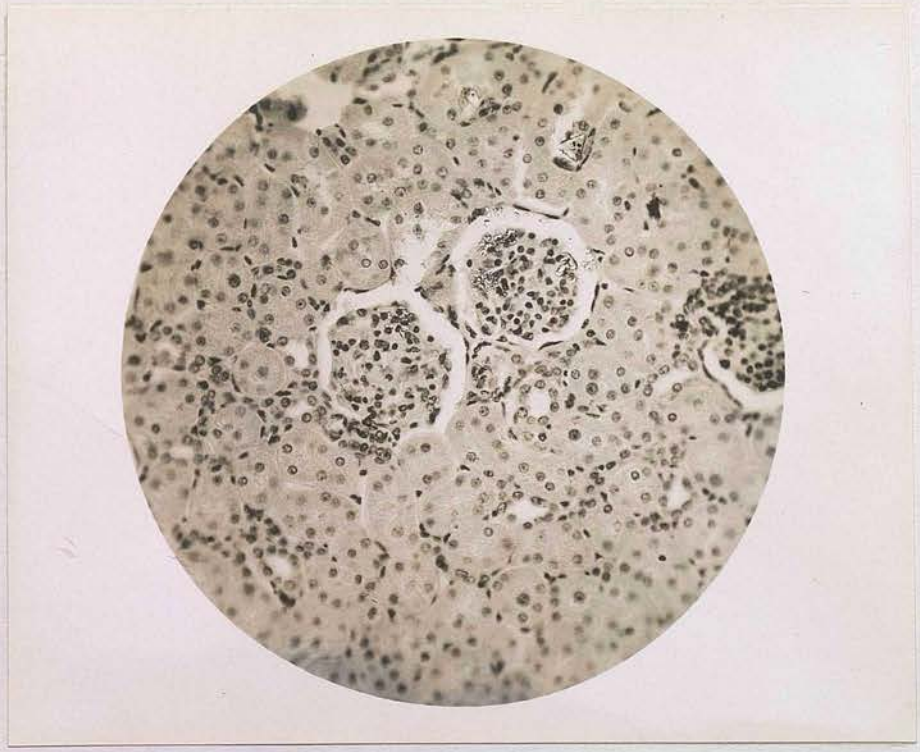


Fig. 26. Rabbit. 3 grams urea added to diet for 7 days. Section of kidney (x260) shows crystals in glomerular capsules. No crystals present in tubules.

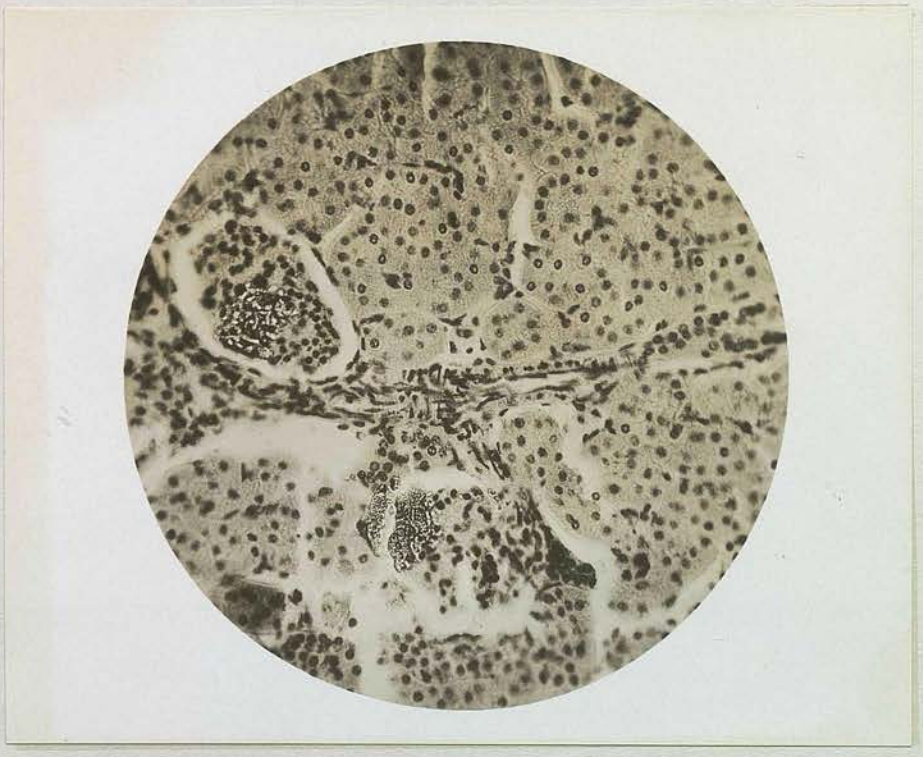


Fig. 27. Rabbit. 2 grams urea added to diet for 7 days. Section of kidney (x 260) shows crystals in glomerular capsules. Tubule cells devoid of urea.

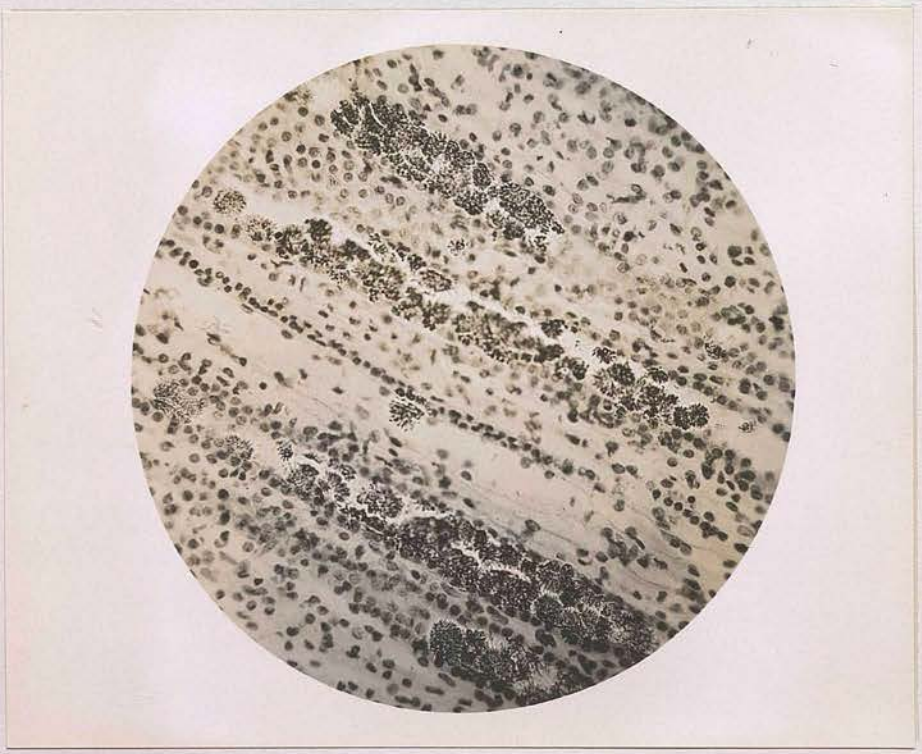


Fig. 28. Rabbit. As fig. 27. Section of kidney medulla (x 260) shows crystals in lumina of collecting tubules.

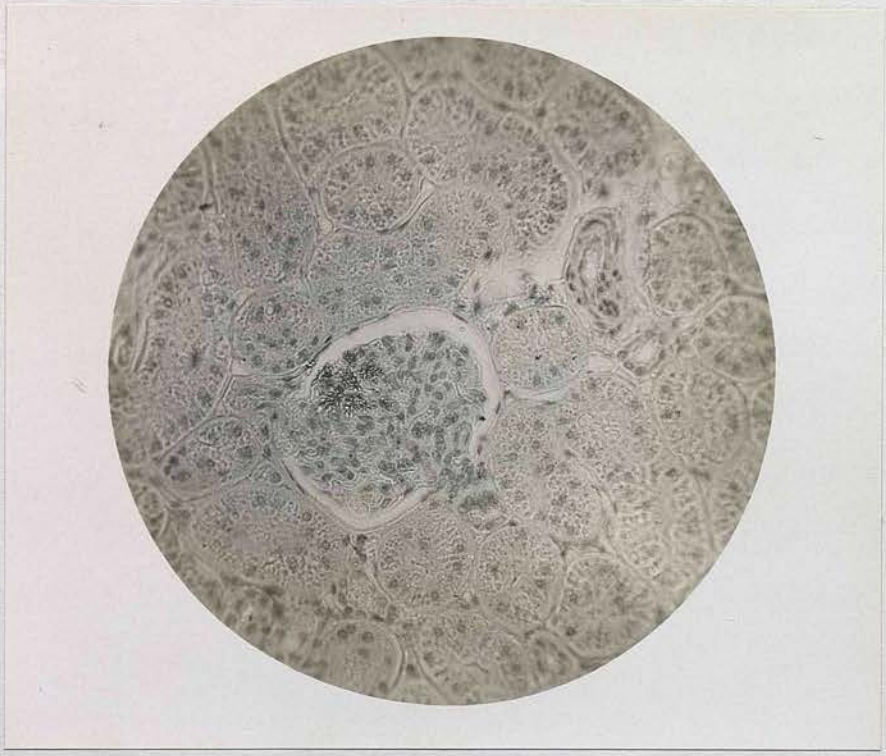


Fig. 2. Cat. Injected with 3 ccs. 5% solution of urea into femoral vein. Killed 20 minutes later. Section of kidney shows crystals in glomerular capsules and interstitial tissue. (x 260)

obtained by the injection method, the high power view of the cortex showing the crystals present in the glomerular capsules and in the interstitial tissue, while the tubular epithelium is entirely devoid of crystals. The low power photograph of the medulla shows the abundant presence of crystals in the lumina of the collecting tubules. The reproductions following the "feeding method" in figs. 25 - 28 show the same findings, the cortical photograph showing capsular crystals present in two glomeruli while the medullary photograph gives a high power view of the crystals within the lumina of collecting tubules.

IN KIDNEY OF CAT AND DOG.

Three cats were injected with 5 ccs. of 5% solution of urea subcutaneously and killed at intervals of 30, 45, and 60 minutes after injection. The crystals were found in the same situations. Two cats were injected with the same amount intravenously and killed 10 and 20 minutes later. Similar results were obtained. (Fig. 29).

Only two dogs were utilised and here the method adopted varied from those of the other experiments. With the animal anaesthetised 10 ccs. of a 5% solution were/

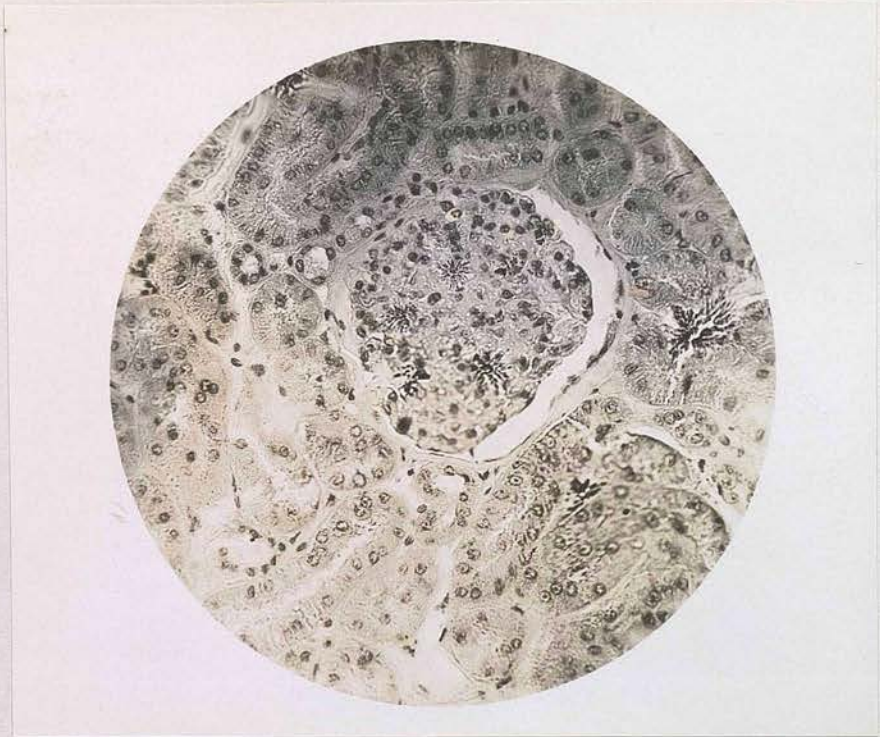


Fig. 30. Dog. Injected with 5 ccs. 5% urea solution into femoral vein. Killed 30 minutes later. Crystals present in glomerular capsules and interstitial tissue of kidney. (x 260).

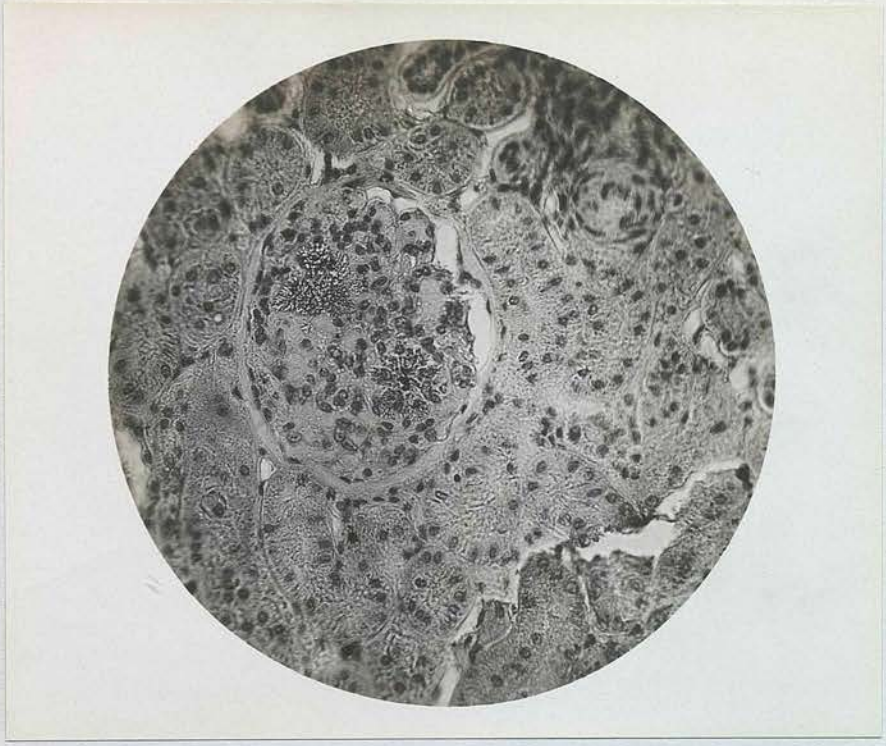


Fig. 31. Dog. Injected with 5 ccs. 5% urea solution intravenously. Crystals present in glomerular capsules and interstitial tissue of kidney. (x 260).

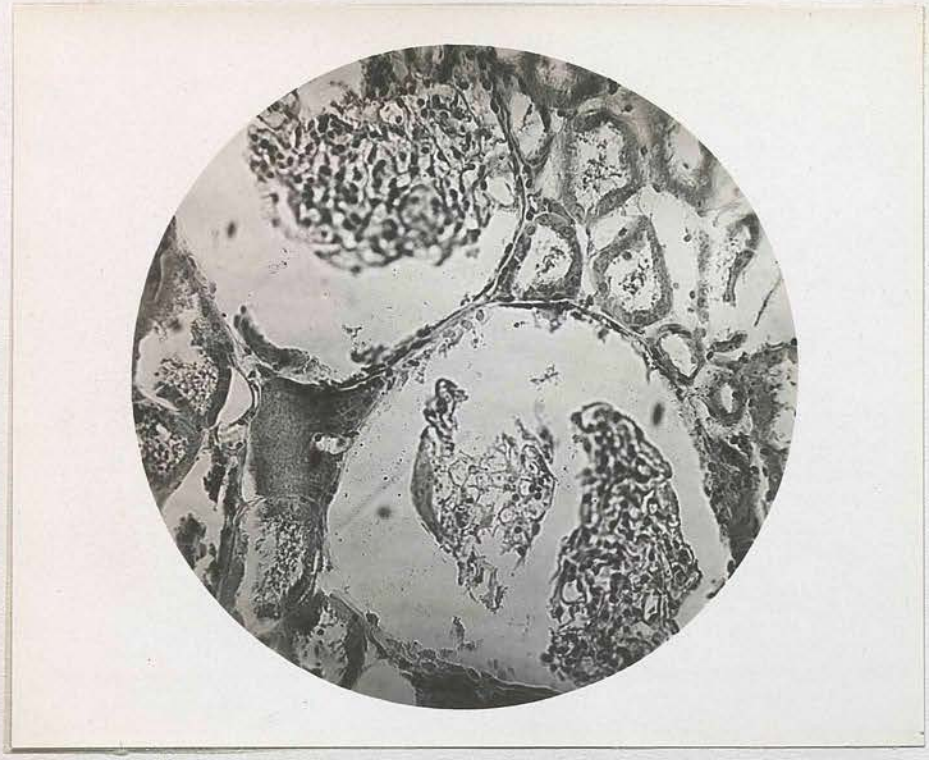


Fig. 32 . Monkey. No urea given. Section of kidney (x 260) shows few scattered crystals in glomerular capsule and in tubule lumina.

were injected through a cannula inserted into the jugular vein. The kidneys were removed 15 minutes later, following upon injection of xanthhydrol solution into the renal artery, and immediately prior to death.

In both of these cases the results obtained were comparable with those of the previous experiments. The striking feature again was the entire absence from the tubular epithelium cells of crystals, which were, however, present in the other parts of the renal tissue. (Figs. 30,31).

IN KIDNEY OF MONKEY.

The kidneys were also removed from one monkey and treated by the xanthhydrol method. No urea was given prior to death, the animal having been used for demonstration purposes. As a result the blood urea concentration was within the normal low limits and consequently very few crystals were observed in the kidney sections. They were seen, however, within a few of the glomerular capsules but none were seen within the epithelium cells of the tubules (fig. 32).

IN KIDNEY OF MAN.

While the above animal studies were in progress, advantage/

advantage was also taken of post mortem material to extend the study to the kidney of man. Two types of case were used for this. The first group consisted of cases of death following upon extrarenal causes, in which the blood urea concentration prior to death was either known or presumed to be normal. Such cases included accidental deaths, pneumonia, tumour of brain, appendicitis and perforated peptic ulcer. The second group comprised cases in which the blood urea concentration was known to be high - in all cases over 100 mgms. % - all (except for one case of congenital cystic kidney) being cases of chronic interstitial nephritis.

In the first group the results obtained were disappointing, the crystals being extremely scanty, so that no conclusive results could be drawn therefrom. They were observed in a few glomeruli and were more abundant in the collecting tubules. No crystals were seen within the tubular epithelium. The results were very similar to those in the one monkey used.

The second group yielded results which were much more easily followed. In all the cases examined, crystals were found within the capsules of the functioning glomeruli, in the interstitial tissue, in the blood vessels and in the tubule lumina. In no case were crystals/

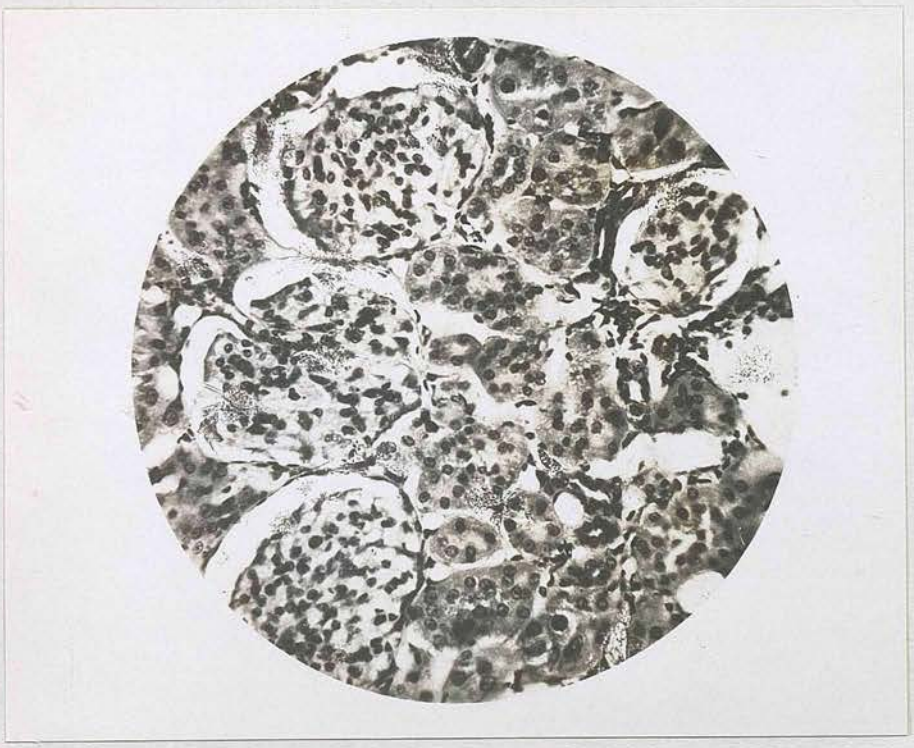


Fig. 33 . Acute parenchymatous nephritis. Blood urea, 68 mgms. per cent. Crystals in glomerular capsules but none seen in tubular epithelium. (x260).

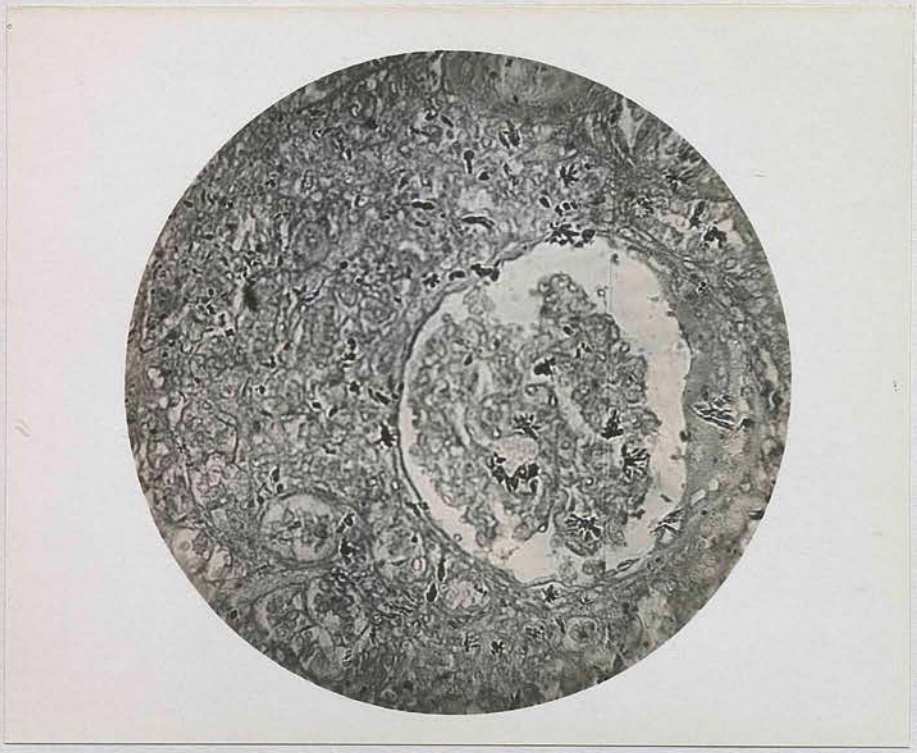


Fig. 34. Mrs. N. (aet.53). Chronic interstitial nephritis. Blood urea, 107 mgms. per cent. Section of kidney showing dixanthyl urea crystals in glomerular capsule and interstitial tissue. (x260)

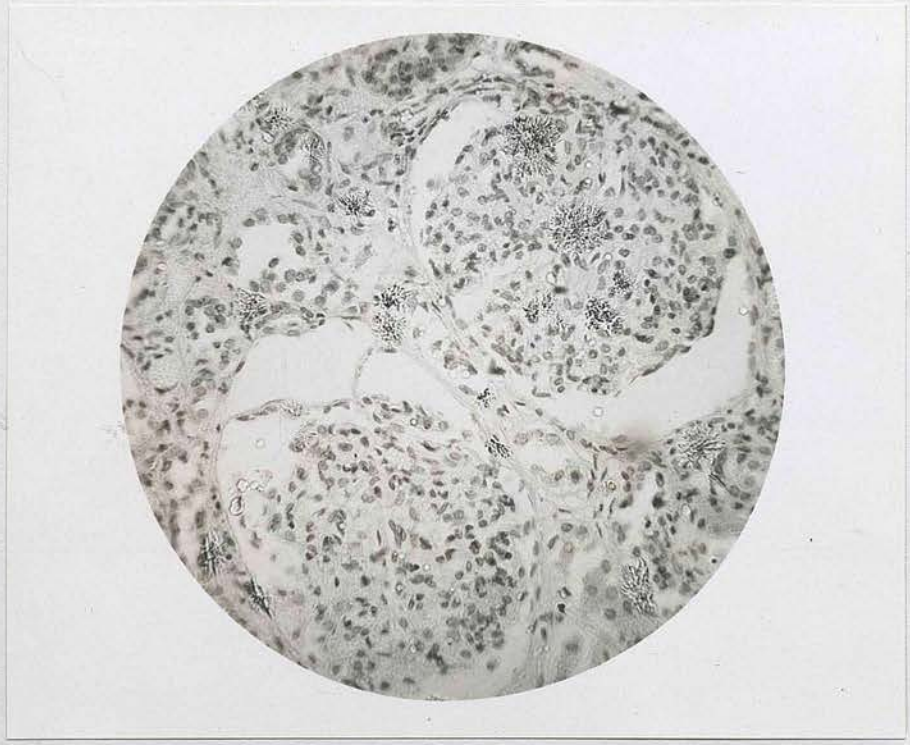
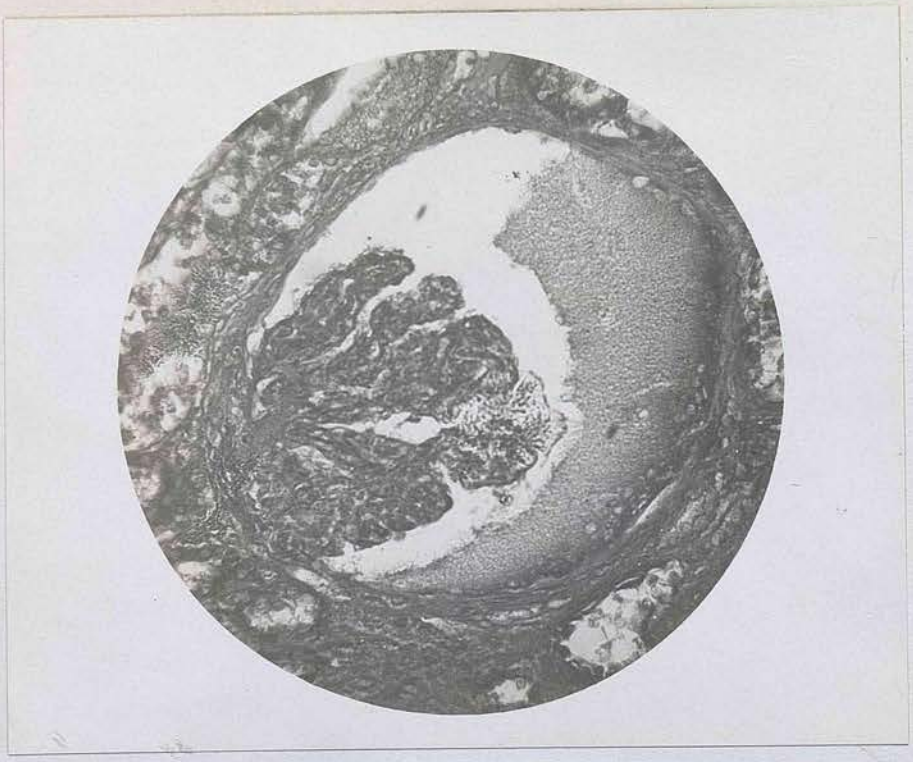


Fig. 35. Mrs. B. (aet.64). Chronic interstitial nephritis. Blood urea, 212 mgms. per cent. Section of kidney shows crystals in glomerular capsules. No crystals in tubular epithelium. (x. 260).



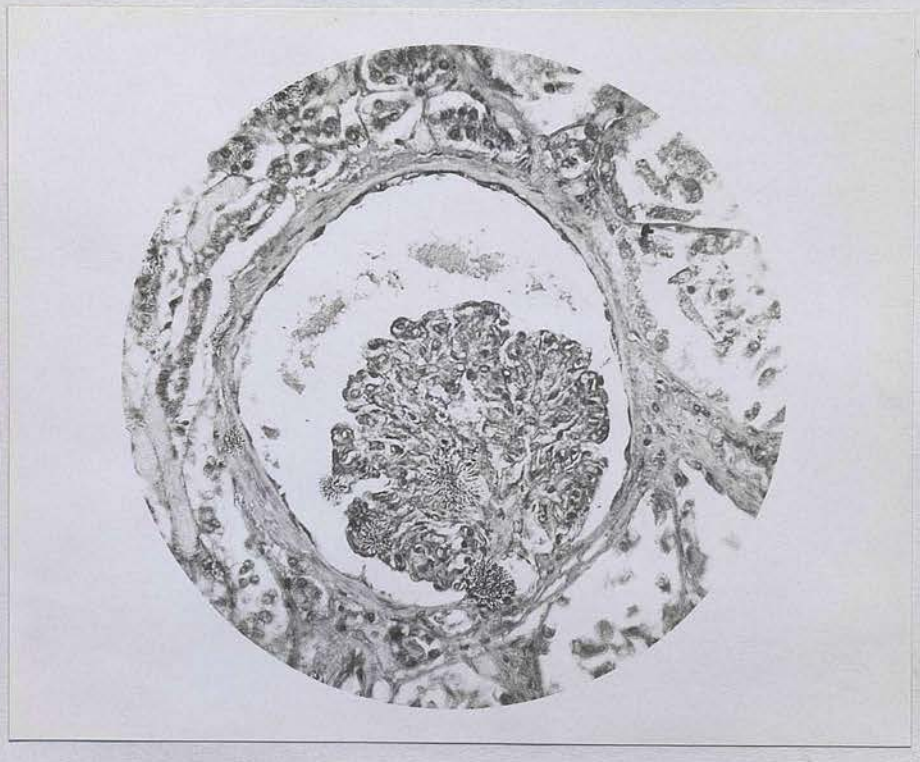
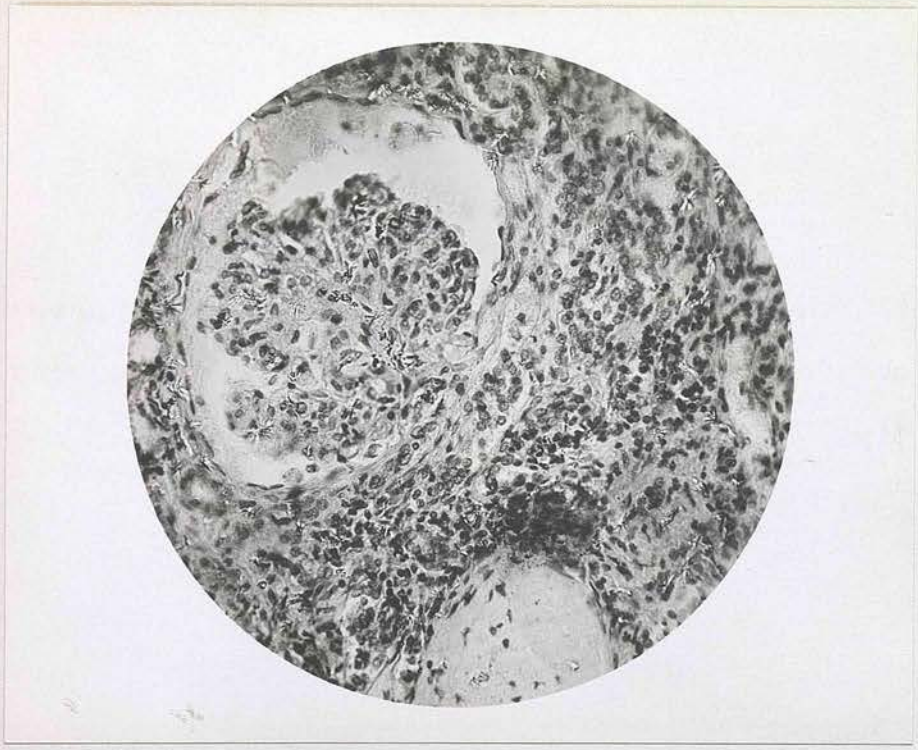


Fig. 36. Mrs. E. (aet. 41). Chronic interstitial nephritis. Blood urea, 162 mgms. per cent. Sections of kidney show crystals in glomerular capsules and interstitial tissue. (x 260).



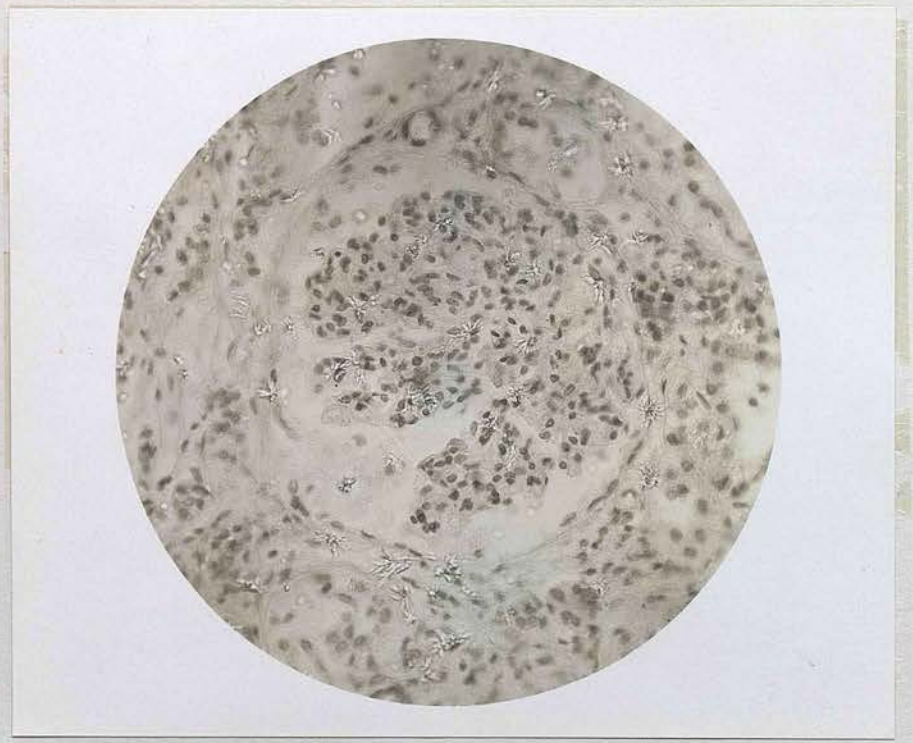


Fig. 37. K.M. (aet.40). Congenital cystic kidney. Sections of kidney xanthhydrol method show interstitial changes. Crystals of dixanthyl urea in glomerular capsules and interstitial tissue. (x 260).

crystals seen within the tubular epithelium cells, and this despite the fact that the crystals were abundant in all the other situations. A series of microphotographs from cases of this second group are reproduced in figs. 33 to 37 .

DISCUSSION.

Two points have to be commented upon following the above study: 1. the comparative value of the different methods used; 2. the mode of excretion of urea.

COMPARATIVE VALUE OF DIFFERENT METHODS USED.

Due to the low concentration of urea in the blood of most animals normally, the method employed is a difficult one to follow if artificial methods are not used to raise the blood content. In the elasmobranchs the blood content is normally high and, consequently, the results obtained in the untreated fish were more satisfactory than in those where artificial heightening methods were utilised. With too much urea present, too many crystals result and it is more difficult to decide on their location.

In the other animals studied the reverse was the case. Normally they had a low blood urea content which showed too few crystals in the kidney section for satisfactory results. Only in the lumina of the collecting tubules were the crystals at all numerous in such sections. In view of this, artificial means of raising the blood urea content had to be adopted. Two such methods were tried in this study:- 1) the injection/

injection method, where comparatively large amounts of urea were administered parenterally over a very short period, the animal being killed shortly after the injection; and 2) the feeding method, where the addition of urea to the diet allowed of a gradual increase in blood urea which lasted over a longer period. Doubtless the blood urea concentration never rose to such high levels in the second method as it would reach in the first.

Both of these methods proved successful in providing a sufficient number of crystals to follow the probable course of elimination. Of the two, however, the feeding method is undoubtedly superior. It provides just a sufficient rise in blood urea to allow for the presence of a satisfactory number of crystals, yet the tissue is never overburdened with them. With injection, however, too sudden and too high a rise in blood urea ensues, and consequently the crystals are too abundant within the section. It would seem that the most satisfactory results are obtained from a moderate rise in blood urea concentration and that such a rise is more likely to follow the oral administration of urea than administration either subcutaneously or intravenously. If these latter routes have to be employed the amount of urea given will require to be much smaller than that employed by previous workers.

The/

The above comment is supported by the results obtained from the use of the kidney of man. In those cases where the blood content was normal the crystals were insufficient in number within the section; in the cases where the blood urea was pathologically high much more satisfactory results were obtained. Of the latter cases those with a high blood urea concentration at death provided almost too numerous crystals, the most successful results being obtained from those with only a moderate rise in blood urea.

MODE OF EXCRETION OF UREA.

Except for the elasmobranchs the results obtained were similar in all the animals used. The difference between these animals and the elasmobranchs is capable of explanation.

In mammalian and frog kidney.

In the animals and in man the urea was seen in the blood vessels, in the glomerular capsules, in the interstitial tissue and in the tubular lumina. It would thus appear that the urea is eliminated from the blood through the glomerular capsule and so reaches the lumina of the tubule. No urea crystals were seen in the tubule epithelium cells of any of these animals. Secretion of the urea by these cells, or absorption by them from the lumen, consequently does not appear to occur/

occur to any great extent. As the blood urea concentration was raised, tubular secretion would undoubtedly be utilised in such cases to eliminate the urea if it did occur. The absence of crystals from the epithelial cells of the tubules showed that no such secretion was occurring in the animals examined. It may be argued, however, that the raised blood urea concentration was the reason for the absence of evidence of absorption, that with a great demand for urea elimination there was no necessity for tubular absorption to return the blood urea concentration to normal limits. Such a statement could be made to explain the absence of intra-epithelial crystals in the injection and feeding methods, but it has to be remembered also that no crystals were seen within the epithelium of those animals in which the blood urea concentration was within normal limits.

In the animals examined it has therefore to be concluded that the urea is eliminated from the blood through the glomerular capsule. No evidence of tubular activity has been observed either of an absorptive or of a secretory nature.

In elasmobranch kidney.

In the elasmobranchs the crystals were found in the situations in which they were present in the other animals/

animals, but in addition crystals were seen within the tubular epithelium cells of some of the fish. It has to be noted, however, that the tubular cells of the first group were clear of crystals. It would thus appear that when the kidney is not exposed to any extra burden the elimination of urea takes place as in the other animals through the glomerular capsule. When, however, a sudden extra demand for urea elimination is made, tubular secretion is called in to assist in the elimination. That the presence of crystals in the cells is more likely to be indicative of secretion than absorption has already been discussed. Absorption is most improbable in the presence of such urgent necessity for excretion.

This difference in mode of function between the elasmobranch and the other animals is most probably dependent upon the different rôle played by urea in the physiology of those fish. As has previously been indicated, urea plays a double part in elasmobranch physiology, providing not only a medium for the excretion of waste nitrogen, but being even more important in the regulation of blood osmotic tension. In the first group of experimental fish urea was being eliminated probably only as a means of evacuation of nitrogen. The environment of the fish was sea water and the blood urea content was unaltered and so presumably/

presumably no osmotic tension change required to be met. In this group the excretion seems to have been entirely glomerular. In the second and third groups osmotic tension was upset by different means, in group two by absolutely increasing the osmotic tension of the blood by injection of urea, and in group three by relatively increasing that tension by decreasing that of the environment. In both of these groups tubular secretion as well as glomerular clearance was noted to be present. It may thus be concluded that in the elasmobranch kidney the normal excretory pathway for urea is glomerular, but that when a heavy excretion is demanded for osmotic tension purposes tubular secretion is also utilised. Tubular secretion acts as an aid to the glomerular activity when heavy demands are made upon kidney function.

CORRELATION OF RESULTS OBTAINED IN MAMMALS AND IN ELASMOBRANCHS.

In view of this possible explanation of the action of the elasmobranch kidney, it might be suggested that the same was applicable to the animal kidney including that of man. As long as the demand on the kidney of man and animals is not great, excretion of urea is glomerular/

glomerular, but as soon as any heavy demand is placed on kidney function tubular secretion will occur. But this suggestion is not borne out by the findings. In the animal experiments a heavy demand was placed upon the kidneys by raising the blood urea concentration artificially; despite that increased demand no evidence of tubular secretion was obtained. In the cases in man, pathological conditions, leading to marked raising of blood urea concentration, resulted in heavy demands for urea elimination; in these cases no evidence of tubular secretion was found. It would thus seem that in animals and in man the glomerular pathway is always utilised for the elimination of urea; under no circumstances is tubular secretion called for as an adjuvant.

This suggested difference of action in elasmobranch and mammalian kidneys calls for further explanation. The increased need for excretion does not appear to be the reason for it, but perhaps the immediate necessity for this excretion may be the cause. In the elasmobranch the elimination of urea necessitates an acute demand being placed on kidney function, otherwise detrimental effects will rapidly ensue within the organism. In the mammalian group no such urgency is present, as no deleterious results are consequent upon urea retention. Thus in the former tubular secretion has to/

has to be invoked to aid glomerular activity in rapidly balancing osmotic tension and so preventing death which would inevitably follow osmotic imbalance. In the mammal no deleterious effects follow upon increased concentration of urea in the blood and so if the glomeruli are incapable of evacuating all the required urea, urea retention in the blood is permitted and tubular secretion is not called for at any time. Even in those dying from uraemia no tubular secretion is found.

It would thus appear that the difference existing between the mode of action of the kidney as regards urea in the elasmobranch and in the mammal is dependent upon the different part played by urea in their physiology. In the elasmobranch the part played is a vital one, and hence urea has to be dealt with urgently, this necessitating secretory activity on the part of the tubule cells. In the mammal urea is inert and its elimination non-vital, and so no additional activity is called for from the kidney following its retention in the blood.

SUMMARY.

1. The theories of kidney function are discussed.
2. The above theories are examined and applied to the excretion of urea.
3. Experimental work directed towards determining the mode of urea excretion is reviewed.
4. The xanthhydrol method - involving precipitation of urea as insoluble crystals of dixanthyl urea - is described.
5. Following review of the literature dealing with the part played by urea in elasmobranch physiology, the xanthhydrol method is applied to ascertain the method of urea excretion adopted in the kidney of these fish. It is suggested that the normal excretion occurs through the glomerular capsule. Any urgent necessity for urea elimination is met by secondary tubular secretion of urea.
6. The method is also applied in the kidney of the frog, rat, mouse, guinea-pig, cat, dog, monkey, and man. In these the excretion is found to be solely glomerular.
7. The discussion concerns the comparative value of the different methods used; and the mode of excretion of urea as elicited by the above experiments. It is suggested that in all instances the glomerular/

glomerular capsule is primarily concerned in the excretion of urea. The apparent discrepancy between the kidney of the elasmobranch and that of the frog and the mammals is attributed to the different part played by urea in the physiology of these animals. In the mammals and the frog urea is utilised as a means of nitrogenous elimination and is excreted by the glomerulus only; in the elasmobranch urea, in addition to its excretory function, is vital for the maintenance of osmotic balance and to this is attributed the secondary tubular secretion, which, under certain circumstances, is added to the primary glomerular excretion.

The above study was carried out with the aid of a grant from the Earl of Moray Endowment for Research, University of Edinburgh.

The experiments involving the elasmobranchs were carried out at the Royal Marine Biological Station, Plymouth; those involving the frog and mammalian kidneys in the Physiology Department, University of Edinburgh. The kidneys of man were obtained from the Pathology Department, Royal Infirmary, Edinburgh.

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II. CLINICAL:-

THE UREA CONCENTRATION RANGE IN THE DIAGNOSIS, PROGNOSIS AND TREATMENT OF RENAL INEFFICIENCY.

DISCUSSION OF KIDNEY FUNCTION.

The theories as to the mode of action of the kidney have already been discussed, but the actual functions served by the kidney require further amplification before the tests for kidney function can be dealt with. Though the mode of action of the kidneys is very doubtful, the functions performed are fortunately more definite.

The kidneys act as the regulators of blood content, being affected by the most minute changes therein. They serve to maintain a constancy in the constituents of the blood and in the amounts of these normal constituents. This function is served by the kidney in several ways:-

1. It is responsible for maintaining the blood and tissue fluids at a constant saline concentration, this concentration varying in different animals. In man, a fluid containing 0.6% NaCl is required, and this saline concentration has to be maintained by the excretion of either chloride or water. Any impaired ability to eliminate either of these substances must be followed by retention of both so that the concentration may not be departed from. The excretion of this water is at the same time of importance in the maintenance of blood osmotic tension. The normal osmotic tension is maintained mainly by the proteins of/

of the plasma, these being normally present to the amount of 6-8 grams per 100 ccs. Of these serum albumin, which is present in greater amount than serum globulin (2:1) and which exerts osmotic tension six times as great, is the most important. As these proteins never appear in the urine normally the maintenance of osmotic tension can only be secured by the excretion or retention of water. In the maintenance of saline concentration both chloride and water excretion play a part; in osmotic tension maintenance water excretion alone is involved. Thus the ability of the kidney to excrete water is of extreme importance in the maintenance of these two, and both are of importance, according to different theories, in the prevention of oedema.

2. The fluid supplied to the tissues has also to be of constant H-ion concentration, the normal pH, 7.4, being maintained by the excretion through the kidney of any substances tending to produce departure from this normal. Numerous other factors are concerned in body pH maintenance, but the kidney plays its part by the excretion into the urine of whichever ion tends to upset the reaction, and thus by the more usual acidic excretion prevents a fall in pH and by the periodic basic excretion prevents a rise above pH 7.4.

3./

3. The function of the kidney upon which most attention is focussed is the part it plays in the elimination of metabolic waste products, the dissolved waste products of metabolism being mainly got rid of into the urine. The most important waste products thus excreted are the nitrogenous products of protein metabolism, especially urea, uric acid, ammonia, and creatinine. These are produced within the body from both exogenous and endogenous protein (except creatinine, which is wholly endogenous) and then are passed into the blood in which they circulate in solution, in small amounts in the normal individual, until removed from it by the kidney. In excreting them from the blood the kidney also concentrates them to varying extents, and in the case of urea this concentration in health may be up to or over 100 times.

4. Normal blood constituents are not eliminated into the urine by the healthy kidney when present in normal amount. When their amount in the blood, however, rises above normal levels, they are immediately excreted. Hence an important part is played by the kidney in ensuring that even normal and useful constituents of the blood are not permitted to produce bodily damage by circulation in increased amounts. Chloride excretion strictly falls under this subfunction, but it is convenient to consider it rather

along/

along with water excretion. The excretion of sugar in hyperglycaemia serves as the best example of this fourth function.

5. Abnormal substances are constantly gaining access to the blood and these the kidney has to eliminate. Examples of such abnormal constituents excreted into the urine are the ketone products of incomplete fat metabolism, bile, bacteria, toxins, and haemoglobin. Dye substances introduced either orally or parenterally have also to be considered along with this group. All of the above mentioned substances are, of course, excreted independent of their amounts in the blood.

In addition to these eliminating functions directed towards maintaining a constant blood composition, the kidney is also believed by some to be capable of manufacturing some substances found in the urine. The production of ammonia by the kidney is easily understood as cellular breakdown consequent upon work is constantly occurring as in other tissues and it is but natural that the ammonia thus produced should pass directly into the urine. There is also abundant evidence of the manufacture of hippuric acid by the kidney from glycine and benzoic acid. The ability of the kidney to elaborate inorganic phosphate from the organic plasma phosphate rests upon less sure foundations/

foundations.

By some it is thought that an internal secretion may also be produced in the kidney and be capable of controlling its function. As yet, however, no positive evidence of such an autacoid has been brought forward and it is most generally presumed that the control of the kidney is non-autacoid in type but is entirely dependent upon the concentration of the different blood constituents, increase or diminution of these supplying the stimulus for their excretion into the urine or for their retention in the blood.

RENAL EFFICIENCY TESTS.

In view of the above functions it is obvious that mere routine examination of the urine is totally insufficient in arriving at a conclusion as to the functional ability of the kidneys. In acute parenchymatous nephritis and in chronic parenchymatous nephritis, examination of the urine may enable one to arrive at a diagnosis, but in neither condition does it indicate the prognosis nor the progress being made by the patient. In chronic interstitial nephritis, urinary examination is of even less help, as until the late stages it aids neither in arriving at a diagnosis/

diagnosis nor in prognosis of the case. Indeed, in this last condition for quite a considerable time the urine passed is absolutely normal both in quantity and content. It is fortunate that this point is now beginning to be realised, as the textbook condition of "marked polyuria and frequency" has much to account for in the late diagnosis of chronic interstitial nephritis. In view of the comparative uselessness of urine examination as indication of functional ability, it is necessary to introduce other means for testing renal efficiency.

BLOOD CHEMISTRY.

As the general function of the kidney can be looked upon as the maintenance of a constancy of blood constituents it might seem that an examination of the blood for especially its nitrogenous constituents might be sufficient. This was first pointed out by Prévost and Dumas (169) in 1821, when they drew attention to the marked rise in blood urea which followed on experimental removal of the kidneys. Christison (102) in 1829 also commented upon the blood and urine urea content, noting that in three of his cases blood urea was increased and urine urea excretion diminished. In 1843, in their original papers, Bright (94) and Rees/

Rees (172) report "the existence of urea in the blood and effusions obtained from the patients" and also in the milk of one patient. Bright (93) had previously (1836) noted a very high blood urea content in a uraemic patient. Picard (165) also emphasised the value of blood urea determinations. Since then numerous references to this have appeared in literature, these being summarised by Polayes, Hershey and Lederer (168), Epstein (110), Chace and Rose (99) and Myers (157). Beaumont and Dodds (88) are of the opinion "that the blood urea and non-protein nitrogen form one of the best guides both to prognosis and diagnosis".

Recently certain observers have suggested that the estimation of the urea content of the saliva may serve indirectly to indicate the degree of blood nitrogen increase (Hench and Aldrich, (129), Calvin and Isaacs (97), and Galan and Houssay (120)). This can scarcely be regarded, however, as a serious contribution to the subject.

Present opinion is unanimous that this increase in non-protein nitrogen occurs in all cases of chronic interstitial nephritis at some stage, it being most generally accepted that uric acid is the first to become increased in the blood, then urea, and lastly creatinine/

creatinine, this order probably being connected with the ability of the kidney to concentrate these substances (Myers, Fine and Lough (159)). This order is, however, disputed by Folin (116). Myers (157) especially stresses the creatinine content, maintaining that a blood creatinine content which is always over 1.5 mgms. per cent. is a sign of renal inefficiency.

Nitrogenous constituents appear to be accepted generally as the most important blood substances for estimation in ascertaining renal efficiency. De Wesselow (204), however, regards the phosphate content as of importance; while Wakefield, Power and Keith (201) suggest that sulphate accumulates in the blood earlier than any of the nitrogenous metabolites. In the hydraemic type of nephritis and nephrosis cholesterol estimation is of value. The literature of this is reviewed by Maxwell (154), and Bloor (90).

Unfortunately in early renal inefficiency it is possible for sufficient kidney substance to be left to meet the daily needs of the body without any of the nitrogenous metabolic waste products becoming heaped up in the blood. Verney (196), reporting on the number of glomeruli in the kidney and the number which are active at one time, clearly shows that it is/

is possible for the kidney to be markedly impaired without any retention in the blood taking place. MacLean (150) and MacLean and de Wesselow (151,152) also support this contention. Beaumont and Dodds (88) note that "some observers state that three fourths of the kidney must be destroyed before nitrogen retention appears". Thus blood examination, while giving help in the advanced cases, is useless in those in which help is most required, for the need is for the diagnosis of deficient kidney function while there is yet sufficient active renal tissue to meet the demands of the body. If an increase in blood nitrogenous constituents is awaited before the diagnosis is made, the case will be too far advanced for beneficial treatment to be adopted.

Though the estimation of nitrogen has been the main blood examination carried out as a test of renal function, the Bachrach-Tittinger test (84), which claims that coagulation time is increased in renal inefficiency , and blood crysoscopy have to be mentioned. No comment upon them is, however, necessary.

CLASSIFICATION OF RENAL EFFICIENCY TESTS.

Blood chemistry being unable to afford definite indication of early impairment of renal function, it has been found necessary to introduce further tests for functional ability. Such tests are each capable of/

of ascertaining the extent of only one of the functions of the kidney and so in most cases a combination of them is desirable to elicit the full functioning power of the organ. To enable an accurate assessment of the degree of functional ability to be made, it will be evident that these tests can only be satisfactory if they are able to call forth the full action of the kidney, bringing the full reserve force of the organ into play to assist what might be termed the rest force which meets the normal demands placed upon the organ.

The multiplicity of tests which have been suggested is indicative of the degree of reliance which can be placed upon most of them. Many, however, were quickly discarded, while the remainder are still held of value in different spheres. Different classifications of these tests could be attempted, but it is convenient here to classify them according to the different subdivisions of kidney function which have been given above. Under this classification the following tests have to be discussed:

I. Tests dependent upon blood volume maintenance.

1. Estimations of blood and urinary chloride content.
2. Chloride test meals.
3. Water tests.
4. Urinary crysoscopy (Koranyi).
5. Electrical conductivity of urine.
6. Estimation of plasma protein content.

II./

II. Tests dependent upon maintenance of blood pH.

1. Estimation of blood pH and CO_2 combining power.
2. Estimation of urinary pH.
3. Alkali test meals.

III. Tests dependent upon excretion of metabolic waste products.

1. Ambard's constant.
2. Urea concentration factor (Gréhant).
3. Provocative urea test of McKaskay.
4. Urea concentration test (MacLean and de Wesselow).
5. Urea clearance test (Moller, McIntosh and van Slyke).
6. Urea concentration range (Calvert).
7. Creatinine tests:
   a)Neubauer; b)Major; c)Holten and Rehberg.
8. Renal test meals (Mosenthal).
9. Uric acid concentration test (Gibson).
10. Specific gravity test (Volhard).

IV. Test dependent upon elimination of normal blood constituents.

1. Diastase test (Wohlgemuth).

V. Tests employing dyes and other substances foreign to blood.

1. Potassium iodide test.
2. Lactose test.
3. Phloridzin test.
4. Sodium glycerophosphate test.
5. Thiosulphate test.
6. Dye tests:
   a)Methylene blue; b)Indigo carmine; c)Phenolsulphonephthalein; d)uroselectan group.
7. Elimination of toxic matter from blood (Bouchard).
8. Excretion of pigment (Thudicum).

VI. Test for"manufacturing" function of kidney.

1. Benzoic acid test.

TESTS/

TESTS DEPENDENT UPON BLOOD VOLUME MAINTENANCE.

Chloride tests.

Examinations for blood and urinary chloride content have been carried out while the ability of the kidney to excrete chloride in response to a known intake has been ascertained. The chloride excretion is, however, dependent upon so many factors besides the kidney, that this mode of testing renal function has now been practically entirely discarded. Alport (81), Adolphe (79), Haldane, Davis and Peskett (123), Pincussen (167), de Wesselow (205), and Rowntree and Fitz (177), all comment upon this test, while Myers (157) gives a fairly complete summary of other work which has been done along these lines. Vallery-Radot (195) and MacLean (150) raise obvious objections to the use of chloride meals as tests of renal efficiency. The observations of Pick (166) which are quoted by Clark (103) have to be commented on in connection with these chloride tests and the water tests which follow. These suggest that a centre may be present in the hypothalamus which is responsible for controlling the passage of water and salt from tissues to blood, posterior pituitary secretion being regarded as exerting its "diuretic antidiuretic" action upon this centre. In this way therefore the renal excretion of chloride and water/

water may be interfered with and so an apparent inability to excrete these substances may be due to the kidney never receiving them to excrete.

The chloride test usually used consists in placing the patient on a diet of fixed chloride content for some days till equilibrium is established. On the day of the test 5-10 additional grams of sodium chloride are given throughout the day and the response ascertained.

Water tests.

In association with the chloride tests the water tests also fall to be considered. These are based on the assumption that in chronic interstitial nephritis the urinary concentration power is impaired and there is resultant necessity to eliminate a large amount of water to get rid of the solid excreta, this large quantity being excreted both by day and night. As already indicated, however, the tendency now is to regard this as a late sign of the condition, and to attempt definite diagnosis long before it has made its appearance. The water tests most used are those of Strauss and Graunwald (191), Volhard and Strauss (198), and Albarron (80), all administering water in known amounts (20 ounces, 1 litre and ½ litre respectively), and then observing the time interval necessary for its full/

full excretion. Normally the full amount is eliminated within three hours. All claim that in renal inefficiency the excretion is delayed. This test is commented on later, as part of the test upon which this study is based employs a modified water test.

Urinary crysoscopy and electrical conductivity.

Though not actual chloride tests, mention must also be made of the use of urinary crysoscopy (Koranyi (138)) and estimation of electrical conductivity of the urine, both of these having been suggested as tests of renal efficiency and both being to a very great extent dependent upon the salt content of the urine. Their use is, however, limited, and so they cannot be regarded seriously as tests for renal efficiency.

Plasma proteins.

The estimation of plasma protein content in nephrosis is of considerable importance in arriving at a conclusion as to the progress of the case. Attention to this was first directed by Epstein (111,112) and since then has been focussed on it by Robertson (174), Rowe (176), van Slyke (187), Bloor (90), Myers (157), Bennett (89), Shapiro (185), Wiemer and Wiener (207), Epstein and Lande (113), and others. Salvesen and Lindes (183) have also pointed out the important relationship between serum calcium/

calcium and the plasma proteins. Whipple (206) has shown the part played by fibrinogen and gives the normal amount of this as .3-.6 grams per cent. As regards an indication of the functional ability of the kidney such examination is, however, of no importance.

TESTS DEPENDENT UPON THE MAINTENANCE OF BLOOD pH.

The power of the kidney to maintain the blood pH cannot be tested for in any satisfactory manner apart from actual estimation of the blood pH itself, and this, with our present methods (even with the glass electrode method of Kerridge (136)) does not seem to be too reliable. Rehn and Gunzburg (173) combined the oral administration of hydrochloric acid and intravenous administration of sodium bicarbonate and estimated the changes in urinary pH. More recently Rosenberg and Hellfors (175) have suggested a test designed to demonstrate the kidney's power of dealing with alkali, but this merely indicates efficiency or inefficiency and does not attempt to distinguish the degree of the latter. They administer 20 grams of bicarbonate orally and expect a resultant rise in urinary pH to over 8 if renal efficiency is present. The/

The estimation of urinary pH forms the index of the Osman (163) alkali treatment for nephritic oedema.

TESTS DEPENDENT UPON EXCRETION OF METABOLIC WASTE PRODUCTS.

Urea tests.

The ability to excrete urea is probably made use of more often than any other kidney test, and is probably more successful. Ambard's constant (82) and the modifications of Ambard and Weil (83), McLean(145,146,147), Walker and Rowe (202), Addis and Watanabe (78), and Austin, Stillman and van Slyke (85), are now generally discarded as they give little information which cannot be obtained from an estimation of blood urea content, and like this estimation they are only of help when an increase of blood urea content is present. In the constant, moreover, only the $\sqrt{4}$ of the blood urea is used. Intended to give mathematical exactness to renal function testing, it unfortunately "o'erleaps itself and falls upon the other" side. Chace and Myers (98) and McLean(145,144,147) used this test but eventually discarded it on these grounds. The urea concentration factor (Gréhant,122) can also be utilised, thus ascertaining the number of times urea has been concentrated from blood to urine. This, however, is made use/

use of during the normal daily renal function and so gives no indication of the reserve force of the kidney. More recently the ability of the kidney to concentrate urea after oral administration has been introduced, the tests thus employed being McKaskay's (142) provocative urea test, the urea concentration test of MacLean and de Wesselow(151,149) and the urea concentration range of Calvert (96). Möller, McIntosh and van Slyke (155) have also based an estimation of kidney ability to excrete urea on a "Urea Clearance Test" where it is suggested that when urine volume is over 2 ccs. per minute urea is eliminated at maximum speed. Again the blood urea content seems to be an unnecessarily important factor. As the present study is concerned with one of these urea tests this group will be further discussed later.

Creatinine tests.

Following earlier work by Neubauer (160), Major (153) suggested the use of intravenous creatinine as a testing substance for the elimination power of the kidney. In this test the creatinine excretion over an hour is estimated, following which 0.5 gram of creatinine is given intravenously. The excretion over each of the succeeding two hours is again estimated. In the normal subject he states that the first of these/

these should show an excretion three times as great as that of the control hour, while the second should be twice as great. This substance has also been utilised by Holten and Rehberg (134), 3 grams being given in 50 ccs. of water orally. Urine and blood are collected over each of the two succeeding hours. The filtration rate over the period is calculated to ascertain the degree of efficiency. Creatinine, being definitely a non-threshold substance, may prove an even more satisfactory medium than urea, which falls to be regarded as a substance of at least low threshold value. If the view of Myers, Fine and Lough (159) be accepted, however, it has to be remembered that creatinine is the nitrogenous product to which the kidney is most permeable and the last which is to be retained by it. In a communication to the Physiological Society of London (June, 1927) the writer reported upon the results following upon the ingestion of creatinine. These included tests carried out upon nephritic patients, but no results of positive value were obtained therefrom. In these experiments only 1 gram of creatinine was given orally.

Renal test meals.

The renal test meal of Mosenthal (156) and Lewis and/

and Mosenthal (140) may be conveniently included in this group. In this test meal, based upon that of Hedinger and Schlayer (126), known food intakes of nitrogen, chloride, etc., are provided at definite hours throughout the day. From 8 a.m. onwards urine is voided every two hours and these specimens are compared especially as regards output, specific gravity, reaction and nitrogenous and chloride content. Mosenthal suggests that in renal inefficiency these two-hourly specimens tend to resemble each other in these respects, and that the night urine, normally much more concentrated, approximates to the day urine in concentration and volume. It is doubtful, however, if these findings characterise the urine in the early stages of renal inefficiency.

Uric acid test.

Gibson (121) records a method for ascertaining the power of the kidney to concentrate uric acid. This is similar to the urea concentration factor of Gréhant necessitating the estimation of blood uric acid and urine uric acid concentrations, the latter then being divided by the former to give the uric acid concentration factor.

Specific gravity test.

As the specific gravity of the urine is mainly determined/

determined by the metabolite content the specific gravity test of Volhard (198) may conveniently be discussed in this section. This test depends upon the variation in specific gravity which results from water ingestion followed some hours later by a meal of normal solid content and accompanied by the minimum of fluid. As, however, the specific gravity of the urine is affected to varying extents by the different solids it contains, it would seem that the test offers an unreliable means of estimating renal efficiency. The comparative frequent combination of diabetes mellitus and chronic interstitial nephritis would be undetectable by this means. Fishberg (115) advocates this test.

TESTS DEPENDENT UPON ELIMINATION OF NORMAL BLOOD CONSTITUENT.

Diastase test.

As a test for renal efficiency the ability of the kidney to eliminate blood diastase is now regarded as of comparatively small importance. It was originally introduced by Wohlgemuth (208) as a renal efficiency test but now serves a more useful purpose as a test for pancreatic efficiency. Only when other organs show advanced disease is the diastase blood content sufficiently increased to call any of the renal reserve tissue into/

into action. Harrison and Lawrence (125) and Comrie (104,105) have recorded results obtained with this test, both ascribing to it only a limited value.

TESTS EMPLOYING DYES AND OTHER SUBSTANCES FOREIGN TO BLOOD.

From time to time different substances which are abnormal to the blood have been suggested for use in tests of kidney efficiency. Of these the potassium iodide, lactose, sodium glycerophosphate, phloridzin, and certain dye tests enjoy some popularity. Of the dye substances methylene blue, indigo carmine, and phenolsulphonephthalein are the commonest. Recently, however, with the increase in pyelography, the administration of substances such as uroselectan and ambridol has been introduced.

Potassium iodide test.

The potassium iodide test is now merely of historical interest, being one of the earliest renal efficiency tests, introduced by Duckworth (108) in 1867. Since then it has been investigated mainly by Continental workers, but is now generally discarded.

Lactose test.

The lactose test of Schlayer and Takayasu (184) has/

has also been dispensed with in most centres. This test comprised the injection of two grams of lactose in 10% solution. The normal kidney should excrete this amount in four to six hours and the presence of lactose in the urine beyond this time was held to indicate renal inefficiency. The test was, of course, based on lactose being an abnormal blood constituent which the kidney immediately excretes.

Sodium glycerophosphate and thiosulphate tests.

The sodium glycerophosphate (Brain and Kay, (92)) and thiosulphate tests (Nyiri (162) and Holboll (133)) are both of comparatively recent introduction and little verification of the tests has been published. Both are abnormal constituents of the blood and their excretion is dependent thereon.

Phloridzin test.

The phloridzin test (Achard and Delamare (77)) is dependent upon the power of that glucoside to produce a temporary lowering of the renal threshold level for sugar. Hypodermic administration of 0.005 gram of phloridzin should, in the normal subject, produce a peak elimination of glucose one hour after administration, and the glycosuria should cease within three hours. Renal inefficiency leads to delay in both of these.

Methylene/

Methylene blue test.

Methylene blue was the first of the better known dye substances to be used in kidney testing (Achard and Castaigne (76)). In the original test 1 cc. of a 5% solution was injected intravenously. The elimination commences within 15-30 minutes and continues normally for at least 48 hours. Delay in onset of elimination or persistence beyond the normal period indicates inefficiency.

Indigo carmine test.

Indigo carmine was the dye used by Heidenhain(127,128) in his experimental investigation of kidney function. Its use for the testing of this function was suggested by Volcker and Joseph (197). 0.8 gram is given intravenously in 4% solution. Normally it appears in the urine within 10 minutes and is mostly excreted within 12 hours although traces may persist up to 24 hours. Renal inefficiency is indicated by delay in onset and prolongation of elimination.

Phenolsulphonephthalein test.

The phenolsulphonephthalein test is now the most widely used of the dye tests. Originally introduced by Rowntree and Geraghty (180) it has met with favourable comment from, among others, Rowntree and Fitz(177), Rowntree, Fitz and Geraghty (178,179), Auld (84), Comrie(104), Snowden (190)/

Snowden (190), Lundsgaard and Moeller (141), and Chisholm (100). 1 cc. of a solution containing 6 mgms. of the dye is administered intramuscularly either into the gluteal region or, as suggested by Comrie, into the arm, the injection being preceded, by 20 minutes, by the oral administration of 500 ccs. of water. Ten minutes are allowed for the entrance of the dye into the blood stream and then 1 hour and 2 hours later the bladder is emptied. The dye content of each of these urines is estimated colorimetrically following alkalinisation. An average excretion of 50-60% during the first hour and 10-20% during the second is looked for in the normal. An excretion of less than 50% over the two hours is generally regarded as pathological.

Excretion pyelography.

As these dye tests have their main application in cystoscopy and ureteric catheterisation the recent uroselectan and ambridol tests may conveniently be considered here. These substances are utilised following administration intravenously for excretion pyelography as their excretion into the urine can at the same time be estimated. They can thus to some extent be regarded as renal efficiency tests (Einhorn, Stewart/

Stewart and Illick (109); Wade and Band (200); Cuthbertson and Jacobs (107), Heritage (130) and others).

The mere mention of two further tests will complete this consideration. As toxic matter is eliminated from the blood by the kidney, Bouchard (91) suggested the estimation of urinary toxicity as a test. Urine as voided was injected into an animal and the less toxic the urine was to the animal the greater was considered the degree of renal inefficiency. It is not surprising that this test has long been discontinued.

Thudicum's test (194) is of interest as pointing towards an advance mentioned at the beginning of this section. In it the colour of the urine was used as an indication of renal efficiency. Yet though this is now discredited as a test, importance is still attached by some to polyuria and specific gravity as indications of early renal inefficiency, although these go hand in hand with the colour.

Test for "manufacturing" function of the kidney.

Only one test has been suggested for the "manufacturing" function of the kidney. As the kidney manufactures hippuric acid from benzoic acid and glycine, Kingsbury and Swanson (137) have suggested the estimation/

estimation of urinary hippuric acid following the oral administration of 2 grams of benzoic acid. They suggest that diminution in hippuric acid formation and excretion are present in renal inefficiency. The difficult technique necessary for hippuric acid estimation is one objection which can be raised to this test.

THE IDEAL RENAL EFFICIENCY TEST.

The ideal renal efficiency test must fulfil certain definite requirements.

1. It must be easy for the physician to apply and
2. easy for the patient to carry out.
3. It must be capable of estimation and interpretation without reference to the laboratory.
4. The substance given must be non-deleterious to the patient no matter what his condition, and at the same time
5. it must be capable of causing the kidney to work to its full capacity so as to allow of estimation of its complete functional ability. Most renal efficiency tests are capable of indicating advanced inefficiency: the ideal test should be able to demonstrate the least departure from normal.
6. It is preferable also that the substance given should be one with which the kidney is normally called upon to deal. This substance should be dealt with only/

only by the kidney and consequently any substance, the excretion of which by the kidney may be interfered with by any other organ or tissue, cannot be held to be a suitable one for application in renal efficiency.

> "We can obtain much more definite knowledge of kidney capacity from noting changes in normal than from determining the existence of the abnormal" (Foxwell).

In considering the claims of the above tests to be regarded as the ideal renal efficiency test it seems that the most generally acceptable substance for such testing is one or other of the nitrogenous bodies.

> "Renal efficiency means above all else the power of the kidneys to eliminate adequately the non-protein or incoagulable nitrogenous bodies, urea, uric acid, creatinine, etc., which accumulate in the blood, not only under ordinary conditions but also under exceptional circumstances of diet, exercise, etc." (Auld)

In most cases the first examination to be carried out is blood analysis especially for the nitrogenous bodies. Various views upon this examination have already been quoted. As, however, blood content is dependent upon the efficiency of other organs besides the kidneys, notably the liver, it would appear that the ideal fluid to examine for evidence of kidney function is the urine rather than the blood. "The amount of nitrogen retention seems to bear little or no relation to the extent of renal damage" (Beaumont and Dodds (88).) MacKay and MacKay (143) give a full account of this/

this and discuss the relationship between the blood urea content and the extent of renal damage. MacLean (150) states that three fourths of the renal tissue can be removed experimentally in animals before increase in blood nitrogen content occurs. Thus while blood nitrogen examinations are of assistance when inefficiency has reached a considerable extent, they are now generally regarded as being unsatisfactory for the detection of early disease.

The chloride excretion tests fail to be accepted as ideal as their elimination is dependent upon so many factors other than the kidney. The kidney only deals with chloride in accordance with the demands of other organs and tissues. In many cases the kidney fails to excrete chloride because it is retained by the tissues and consequently the kidney never receives it to excrete. The work of Pick (166) bearing upon this point has already been commented upon. A further objection to the chloride tests lies in the inability to administer sufficient chloride to call forth the full reserve force of the kidney without injurious effects being produced upon the patient.

Similarly with the diastase test its excretion is dependent entirely upon its amount in the blood and this amount is controlled by hepatic and pancreatic activity. Consequently if these two organs are to play/

play the primary part and the kidney only a secondary one, the excretion of diastase by the kidney cannot be regarded as giving a true indication of renal efficiency. Also no means has yet been provided of artificially increasing the amount of diastase circulating in the blood to such an extent as to cause the kidney to function "all out" in excreting it into the urine.

The dye and similar tests can also be excluded as ideal functional tests. Rowntree and his co-workers (77-81) and Auld (84) all regard the phenolsulphonephthalein test as superior to all other tests "due to its ease of application, its rapidity of action and its reliability". It, however, has to be remembered that the substance utilised is one which the kidney is not normally called upon to deal with, and consequently it is not the most suitable one for use for this purpose. Its estimation also calls for a method not utilisable by the general physician. Auld's advocacy of the phenolsulphonephthalein test seems strange in view of his expressed opinion already quoted that "renal efficiency means above all else the power of the kidneys to eliminate adequately the non-protein, or incoagulable nitrogenous bodies - urea, uric acid, creatinine, etc." Beaumont and Dodds (88) regard the test as "very satisfactory provided there is no blood in the urine".

Comrie/

Comrie(104)suggests that its use is a wide one and that with it valuable aid in prognosis can be obtained. The test, however, fails to fulfil the requirements of the ideal. It fails to bring out the full action of the kidney; it requires laboratory estimation; and it is an unnatural substance with which the kidney is called upon to deal.

The substances which suggest themselves as likely to be most successful in testing for renal efficiency are the non-protein nitrogenous bodies which are normally produced within the body from protein metabolism and normally circulate in the blood to be excreted from it by the kidney. The healthy kidney eliminates these practically as soon as they appear in the blood, and their amount in the urine is directly dependent upon their concentration in the blood. Consequently anything leading to an increase in their blood content should immediately give rise to increased action on the part of the kidney with resulting increased excretion into the urine. The three substances belonging to this group which are at present used in testing kidney efficiency are urea, uric acid and creatinine. The last has only recently been suggested for use by Major (153) and Holten and Rehberg (134) and as yet little work has/

has been done with it and so little experience has been gained of its excretion. In the writer's experience little information was obtained from the study of blood and urinary creatinine following administration of 1 gram doses. As a non-threshold substance, however, it seems probable that its elimination after oral or parenteral administration should give rise to an accurate indication of renal efficiency. Unfortunately its estimation has to be done by a laboratory method and so this test is not ideal as regards "ease of estimation and interpretation". The same objection is raised to the uric acid concentration test suggested by Gibson(121).

UREA AS A SUBSTANCE FOR KIDNEY TESTING.

The importance of urea excretion as an indication of kidney function has long been recognised. Frerichs (119) observed the low urea excretion present in chronic nephritis and reported on it in 1851. In 1890 Cruise (106), writing on ureametry, states that "the importance of ureametry is far greater than the testing for albumin because, while the latter is often present and signifies little/

little and may be absent in very grave cases, the quantity of urea is always a matter of serious, and often of vital, consequence". Unfortunately, as is pointed out by Langdon Brown (95), the mere estimation of urine urea content is of little value if the protein intake is not considered along with it.

Even considering this, however, and remembering the large reserve power of the normal kidney, it is possible for that organ to be markedly damaged and yet be capable of eliminating all the nitrogenous waste matter which is produced from the exogenous protein and from the tissue breakdown within the body. If such a kidney be required to deal with a known amount of nitrogenous waste matter which will call for a full action of kidney tissue its inefficiency will become demonstrable. It will be incapable of concentrating urea to the extent carried out normally and consequently while urinary concentration will be lower than normal the amount remaining in the blood will be greater than that found with an efficient kidney.

UREA TESTS COMMONLY EMPLOYED.

The first tests which utilised urea for this purpose were those of McKaskay (142) and MacLean and de Wesselow/

Wesselow (49,67). In their original paper the latter writers suggested "that the loss of power to concentrate urea may not be easily detected in ordinary specimens of urine but can be readily brought out by giving urea". They recognised that the kidneys possess tissue largely in excess of the amount required for body functions and that these kidneys might suffer considerable damage and yet retain sufficient renal substance to meet normal functions. They suggest the administration of 15 grams of urea in the morning, fluid intake having been restricted during the preceding day. Following urea administration the bladder is emptied one and two hours after and the urea content of each sample of urine is estimated.

> "If the percentage of urea exceeds two, the kidneys may be taken as fairly efficient: if below two, the content is unsatisfactory and the lower the concentration the more serious the lesion"..."Many moderately severe cases are unable to concentrate to more than 1.4-1.5%" (MacLean and de Wesselow, 151)

Thus the test is unfortunately only successful in those cases in which the kidney damage is fairly advanced. Jones and Cantarow (135) modified this test. Harrison (124) placed a slightly different interpretation upon the results obtained with this test, requiring a concentration exceeding 2.5% for "normal" and a check blood urea before considering a concentration between 2% and 2.5% "normal". He states "normal", however, as/

as "probably more than one quarter of the total kidney tissue was functioning on the day of the test". If the concentration is below 2% "it may be due to an artefact, or the renal condition may be definitely unsatisfactory, less than one quarter of the kidney functioning". The definition of "normal" seems the all important condemnation of the test. If the test can only demonstrate renal inefficiency when three fourths of the tissue have been destroyed it is far from ideal. The ideal must be able to demonstrate the least departure from the normal. When asked to act to full capacity the kidney is capable of concentrating urea to at least 4% in the urine, and consequently if the kidney should be capable of concentrating to this extent a forced concentration of 2% cannot possibly be indicative of renal efficiency. Hence as MacLean and de Wesselow's test fails to bring out the full functional ability of the kidney it cannot be accepted as the ideal kidney efficiency test. Part of the reason no doubt lies in the fact that the kidney is asked to concentrate its urea by day whereas of course its concentrating action is normally much greater during the night. Calvert's urea concentration range employs night concentration instead of day concentration and consequently the result/

result obtained is more likely to approach to the full functional ability of the kidney.

UREA A NON-DELETERIOUS SUBSTANCE TO BODY TISSUES.

Urea satisfies as a substance for utilisation in kidney testing in that, as far as is known, it is non-deleterious to body tissues in reasonable amounts. It is now known that urea itself plays no direct part in the production of uraemia. Hewlett, Gilbert and Wickett[31,32] have definitely shown that except when exceptionally large doses are being given over a short period no ill effects are produced. Following the administration of 100 grams of urea in one dose Hewlett obtained a urea concentration in the urine of 3.77%, while following 125 grams in four hours a urinary concentration of 4.2% was obtained. Gilbert showed a urine urea content of 6.43% following 100 grams given over three hours. Definite symptoms occurred similar to those of asthenic uraemia: headache, dizziness, drowsiness, bodily weakness and fatigue. In the writer's experience no such symptoms were felt following the oral ingestion of up to 60 grams in one dose, the only symptoms then experienced being those of thirst, polyuria and frequency. In pathological conditions administration/

administration of up to 25 grams of urea in one dose has not been attended by any increase in symptoms. Numerous writers have reported uraemic-like attacks following the experimental administration of large amounts of urea to animals (Leiter(139), Streicher(192)). It has to be remembered, however, that the individual factor has also to be considered in relation to this - some cases showing uraemia with little or no increase in nitrogen content of the blood, while others have no signs of uraemia when their blood urea has risen well into three figures. The present opinion seems to be very definitely that urea is not the actual cause of uraemia. It would thus appear that as far as being non-deleterious to the patient is concerned, urea is capable of application in the ideal renal efficiency test.

ESTIMATION OF URINARY UREA CONCENTRATION.

The estimation of urea in the urine may be either a simple matter or a much more complicated one dependent upon the method of estimation which is used. If the urease method be employed, the result, while said to be slightly more accurate, can only be obtained by a laboratory test. Using the sodium hypobromite method, however/

however, though the result is generally regarded as slightly less accurate, it nevertheless is at least 90% correct and this result is obtainable by a method which can be carried out by any busy practitioner and interpreted without any laboratory reference. The sodium hypobromite solution can also be easily and quickly prepared so that no low result need occur from use of stale solutions. A convenient method of preparing small amounts of sodium hypobromite solution is appended*. Foxwell(8)employed this method and found that it gave "92% of the total nitrogen in the urea, the remaining 8% being converted to cyanates; on the other hand, it gets some 2% from creatinine, uric acid, etc., so that on the whole the nitrogen obtained is about equal to 94% of that existing in the urea". Powweather(7)also defends this method of estimation. Though only a 94% accuracy can be obtained the ease of the method is its great recommendation, it being possible for/

*A. Sodium bromide 62.5 grams
Bromine 20 ccs.
Distilled water 500 ccs.

B. Sodium hydroxide 22.5% (S.G. 1250).

C. Distilled water.

To prepare solution of sodium hypobromite mix equal volumes of A, B, and C. A Doremus ureometer requires 25-30 ccs. of the above solution.

for the 5 specimens requiring estimation in the urea range to be done in 15 minutes and so within the reach of even the busiest practitioner, whereas with the urease method much more time must be expended and a more elaborate apparatus used for estimation, considerations rendering it outwith the sphere of the practitioner. It is also very greatly to be doubted if, even in the hands of experienced technicians, a greater accuracy than 94% is constantly obtained by this method. Certainly in the experience of the writer the value of increased efficiency, if any, in the urease method has been far outweighed by the ease and rapidity of application of the sodium hypobromite method. Control experiments have been carried out upon solutions of urea of unknown concentrations falling within the limits of those normally encountered in urine. The urease methods employed were those of Folin (116) and Taylor (193), utilising both fresh soya bean urease (Folin (116) and van Slyke and Cullen (188,189)) and Dunning's tablets. In no respect did the result warrant the abandonment of the sodium hypobromite method. Greater accuracy was never attained, and the time expended was much greater. If the urease method be considered essential the urea tests must cease to be regarded as possible ideal renal efficiency tests. The urease method is certainly not "capable of application and interpretation/

interpretation without reference to the laboratory". In the present series both urease and hypobromite methods were used in the beginning but the former method was very soon abandoned.

In the writer's opinion the urea tests advance the greatest claim to be regarded as ideal. It is admitted, of course, that they test one function of the kidney only, but this function is that for which a test is most required, being a function which must go on and one which does not show any easily detected sign of impairment. Upset of water excretion quickly shows by oedema, while the excretion of abnormal blood constituents is a function comparatively rarely called upon. But nitrogen excretion is constantly required, and interference with this function does not demonstrate itself until the degree of inefficiency is so great as to be practically terminal. By many renal inefficiency is regarded as synonymous with inability to excrete nitrogenous waste.

THE UREA CONCENTRATION RANGE OF CALVERT.

In the present series of cases the test used has been one of the nitrogen excretion tests, Calvert's Urea Concentration Range. This test was only adopted after/

after comparison with the other renal efficiency tests. Of these the diastase and MacLean and de Wesselow's urea concentration test were quickly discarded, while later the phenolsulphonephthalein test was also dispensed with. Thereafter the urea concentration range and examination of the blood for non-protein nitrogen, urea and creatinine were used, the latter merely as a check upon the former. Only in exceptional cases were the phenolsulphonephthalein and urea concentration tests later utilised, in cases where the urea concentration range seemed opposed to the clinical findings. These cases and the findings in them are discussed later.

In examining the cases the test was applied and interpreted without reference to the clinical condition, the findings being later correlated with those obtained clinically. The clinical examination comprised full urinary examination including that for casts, cardiovascular examination for evidence of hypertrophy of the left ventricle, estimation of blood pressure, ophthalmoscopic examination and, in the males, prostatic examination.

Method/

Method adopted in application of test.

The method of applying the test was that originally suggested by Calvert(96), but slightly modified to fit in with hospital routine, and also with the individual findings in the different cases. The amount of fluid was restricted from midday onwards. At 9 p.m. the bladder was emptied and 15 grams of urea, dissolved in 100 ccs. of water, were given. At 10 p.m. the bladder was again emptied and this specimen, hereafter referred to as specimen A, was kept for estimation. It gave little information, but allowed for the immediate diuresis which the administration of urea so often produced. From 10 p.m. to 6 a.m. the patient was allowed to concentrate upon the urea given, and at 6 a.m. the bladder was emptied (Specimen B2). If any urine had been passed prior to 6 a.m. it was kept and estimated (Specimen B1). At 6 a.m. two pints of fluid were given, usually as tea and water, and the bladder later emptied at 7 a.m. (Specimen C1) and at 8 a.m. (Specimen C2). If no diuresis had occurred by 8 a.m. a further specimen (Specimen C3) was taken at 9 a.m. No breakfast was given until the completion of the test.

Amount of urea given.

The amount of urea given, 15 grams, was that suggested/

TABLE I.

Maximum urinary concentrations with varying urea intakes.

	Grams of urea.								
	5gms.	10gms.	15gms.	20gms.	25gms.	30gms.	50gms.	60gms.	Remarks
J.D.S.C.	1.6%	2%	3.8%	3.9%	3.8%	3.9%	3.7%	3.6%	Normal kidneys.
Mrs. McV.	-	-	4.2%	4.3%	4.2%	-	-	-	Normal kidneys.
Mrs. L.	-	-	2.6%	2.6%	-	-	-	-	Chronic interstit nephritis.

suggested by Calvert and is the same as is used in MacLean and de Wesselow's test. Before adopting it, however, the response of the kidney to larger and smaller amounts was ascertained personally and upon patients. Typical results obtained with varying amounts of urea are shown in the table on the opposite page. From this table it will be seen that 15 grams is sufficient to produce the "all out" action of the kidney. When smaller amounts were used a less concentration in the night urine was obtained, but using larger amounts it was found that there was no increase in the concentration, the extra urea being got rid of by an increased excretion of water. When 60 grams were taken the result is best described as "nightmarish", dreams of dehydration alternating with waking moments for urination. The dehydration probably accounted for the lower concentration with the larger amounts than with 15 grams. In all instances fluid intake was curtailed from noon of the previous day as is done when the test is applied. Harrison (24) is opposed to this view, stating that "15 grams may not always be sufficient to provoke a concentration greater than 2% although the kidneys be efficient". This opinion, however, is expressed regarding the urea concentration test/

test of MacLean and de Wesselow and so is concerned with day concentration. In view of these results it is of interest to refer to the work of Hewlett, Gilbert and Wickett(31,32). These workers observed the effect of administration of large doses of urea upon blood and urine urea concentrations. Doses up to 125 grams over 4 hours were given with resultant symptoms of "headache, dizziness, apathy, drowsiness, bodily weakness, and fatigue - similar to asthenic uraemia". In the writer's experience with a single dose of 60 grams no such symptoms were experienced. F.C.McLean expresses much similar views, "the occurrence of a high blood urea concentration is not necessarily accompanied by symptoms of uraemia". In the series of experiments of the first-named workers, the urine urea concentration varied from 3.77% to 6.43%, the average concentration over the 5 quoted experiments being 4.91%.

As no increase in urinary concentration was obtained with larger amounts, 15 grams was used as the standard dose for first application of the test. In a few instances where the result apparently contradicted the clinical findings a repetition was carried using 20 grams. In no case was a revision of the findings thereby necessitated.

Under/

Under the age of 14 only 10 grams of urea were administered. The urinary concentration obtained thereby was the same as in the adult with 15 grams. In two cases the amount given was increased to 15 grams with no resultant increase in concentration:

C.B., female, aet.12. 10 grams, 3.7%; 15 grams, 3.8%
E.W., male, aet.8. 10 grams, 3.65%; 15 grams, 3.6%.

Necessity for restriction of fluid intake.

The restriction of fluid intake from midday onwards is a second important point in the application of the test. If it be not observed, there is less likelihood of the "all out" action of the kidney being obtained, and instead of a true maximum concentration a false maximum is obtained consequent upon the resultant increased output of water. Harrison (124) drew attention to this point in dealing with the MacLean and de Wesselow test and advocated the withholding of fluid for at least 6 hours before application of the test. Rabinowitch (207) also emphasised this necessity for fluid restriction prior to the application of urea tests. The drinking of fluid during the night has especially to be guarded against in the urea range. Indeed the association of a lowered maximum concentration with diuresis should not be accepted as evidence of/

TABLE II.

Age Period	0-10	10-20	20-30	30-40	40-50	50-60	over 60
Male	1	3	8	16	9	7	6
Female	2	6	10	7	8	17	8
Average maximum	3.8%	3.8%	3.8%	3.9%	3.7%	3.7%	3.5%
Average minimum	0.3%	0.35%	0.4%	0.4%	0.4%	0.4%	0.45%

Table showing average urea range figures over varying age periods.

of renal impairment without reapplication of the test with verification of the previous findings.

THE NORMAL UREA CONCENTRATION RANGE.

In order to obtain results which could be taken as normal, the urea concentration range was first applied to cases in which no renal inefficiency was anticipated, this part of the study comprising 108 cases. The subjects selected were patients receiving treatment in the wards for some condition which was unlikely to bear any influence on renal function. In addition the test was also applied to a number of individuals who were apparently in perfect health and engaged in their normal occupations. The ward cases and healthy volunteers were of both sexes and of varying ages, and so it was possible to strike a standard in accordance with both sex and age. The results obtained are seen by reference to the Table on the opposite page. From this it will be seen that the average maximum concentration is between 3.5% and 4% while the average minimum concentration varies between 0.25% and 0.4%. Sex has no effect upon these averages, while age has comparatively little influence. The youngest patient tested (aet.4) showed a range of 4% maximum and 0.2% minimum/

minimum, while the oldest (aet.83) showed a range of 3.4% maximum and 0.45% minimum. In the complete series the highest urinary urea concentration obtained was 5%, this figure being found in 1 male and 1 female. In all only 12 concentrations exceeded 4%. These figures are of interest when noted with the figures obtained in the experiments of Hewlett, Gilbert and Wickett (31,32) already quoted. Samson Wright (209) states that "normal kidneys may concentrate to 4% or over".

Amounts of urine passed during "normal" test.

In addition to the concentration of urea, the amounts of urine passed in the different stages of the test were noted. The immediate response to the administration of urea varied with the individual but up to 10 ounces (300 ccs.) were passed in the hour elapsing after its administration. This amount varied inversely with the concentration. During the eight hours of the maximum concentration period up to 15 ounces (450 ccs.) were passed. With a 3.5% concentration this allowed of the excretion of 15.75 grams of urea over that period. Following the administration of the fluid, up to 10 ounces were passed during the first hour and up to 20 ounces over the second hour/

THE UREA CONCENTRATION RANGE.

Fig. 38.

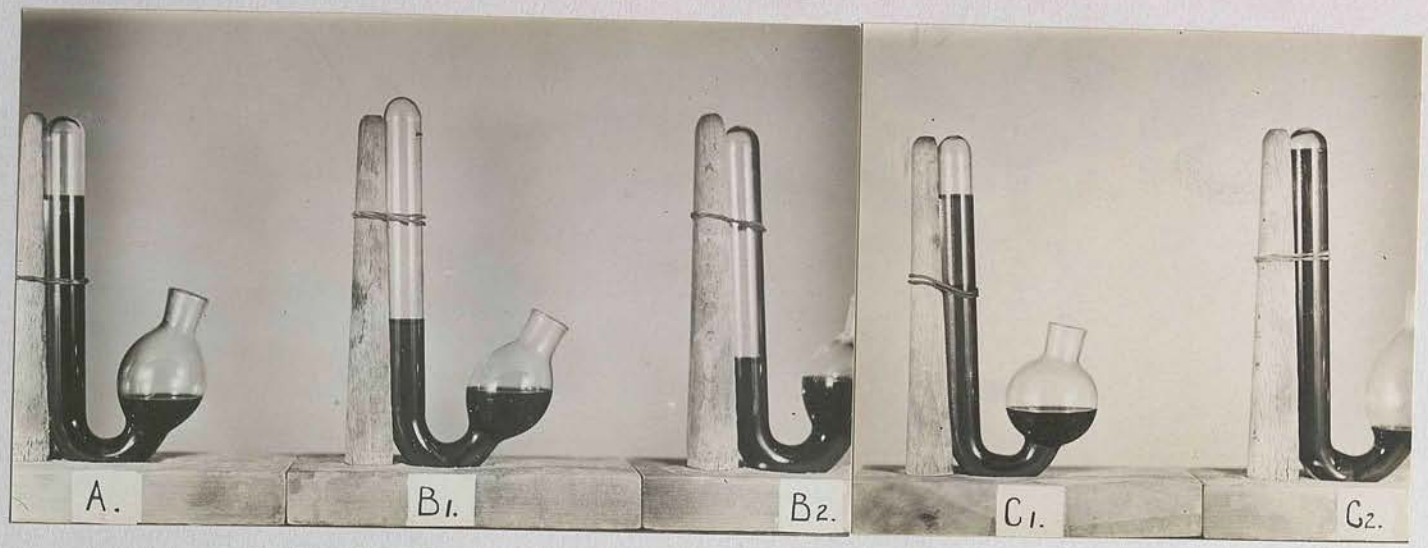


TABLE III.

NORMAL UREA CONCENTRATION RANGE.
Mrs. S. B.687 Ward 30 R.I.E. 24.vi.27.

A.	6 ounces	1.4%
B1.	7 ounces	4%
B2.	4 ounces	3.8%
C1.	7 ounces	0.8%
C2	14 ounces	0.3%

Maximum, 4%; minimum, 0.3%

Note: For photographic purposes, urines B1 and B2 have not been diluted as is customary when estimating.

hour. If the third hour urine was also taken it was found that the whole of the fluid given could easily be accounted for over the three hour pericd. In this respect the findings were similar to those obtained by Strauss and Grunwald in their water test. As will be noted later, these amounts showed variations when pathological conditions were present. A typical urea concentration range, both as regards amounts and concentrations, is shown in fig. 38 and Table III .

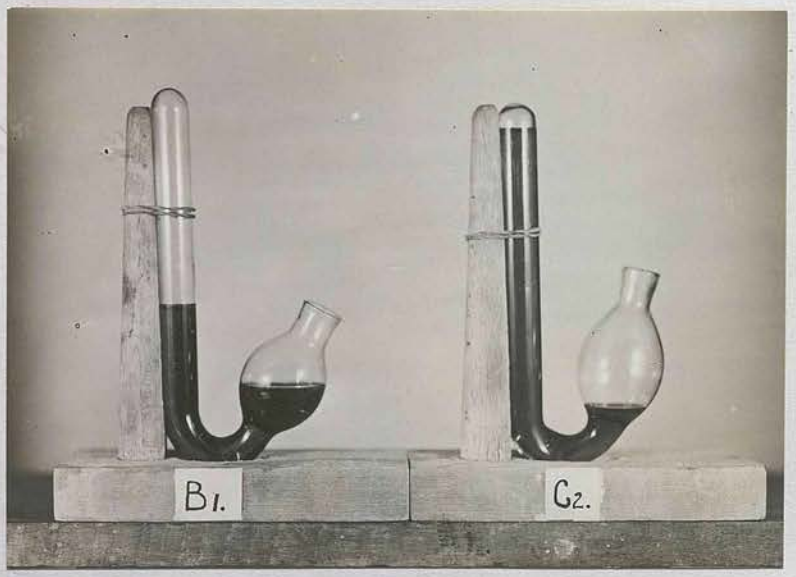
THE UREA CONCENTRATION RANGE IN PATHOLOGICAL CONDITIONS.

With the establishment of the normal urea concentration range as maximum, 3.5-4% and minimum, 0.3-0.4%, the study was carried to cases in which renal inefficiency might be present, 504 patients being investigated in this way. The cases employed were mainly those in which high blood pressure was found, the test being utilised to discriminate between those of renal and non-renal origin. In addition it was applied to all forms of kidney disorder, (acute parenchymatous nephritis, chronic parenchymatous nephritis and nephrosis, chronic interstitial nephritis, orthostatic albuminuria, pyelitis, tuberculous kidney, haematuria, etc.) to cases/

THE UREA CONCENTRATION RANGE.

Hyperpiesis - no renal inefficiency.

Fig. 39.



Mrs. A.
Urea concentration range:
Maximum, 3.8%; minimum, 0.35%.

cases of prostatic involvement, and in cardiac failure. Its value in diagnosis can be conveniently followed in that order.

VALUE OF THE UREA CONCENTRATION RANGE IN DIAGNOSIS.

Diagnosis of hyperpiesis and chronic interstitial nephritis.

In these cases in addition to the urea range, full blood examination, urinary examination, clinical examination for systolic and diastolic blood pressure, condition of heart, signs and symptoms of uraemia and ophthalmoscopic examination were utilised. If necessary a second renal efficiency test was applied, and in the event of death a post mortem examination was obtained wherever possible.

It can be stated with confidence that the test is of great value in distinguishing high blood pressure of the primary hyperpietic type and that due to chronic interstitial nephritis. In the first group the kidneys are unaffected and the urea range shows normal figures (fig. 39) This group corresponds with the "benign form—hypertension without renal insufficiency " of Fahr (114) and "the benign or stationary sclerosis without a tendency to become renal" described by Volhard (199). In the chronic interstitial nephritis group the figures obtained/

obtained varied with the degree of the disease but always showed some departure from normal. This group comprises the malignant hypertension form of Fahr; and the second and third groups described by Volhard, these being respectively advanced sclerosis of long duration which has resulted in renal atrophy and inefficiency, and rapid sclerosis which soon terminates in uraemia. In early cases the maximum showed a fall below 3.5% with no associated rise in the minimum. As the condition advanced the fall in maximum concentration continued and became associated with a rise in the minimum concentration, until in advanced cases there was approx-imation of the maximum and minimum concentrations.

Stages of chronic interstitial nephritis as shown by the Urea Concentration Range.

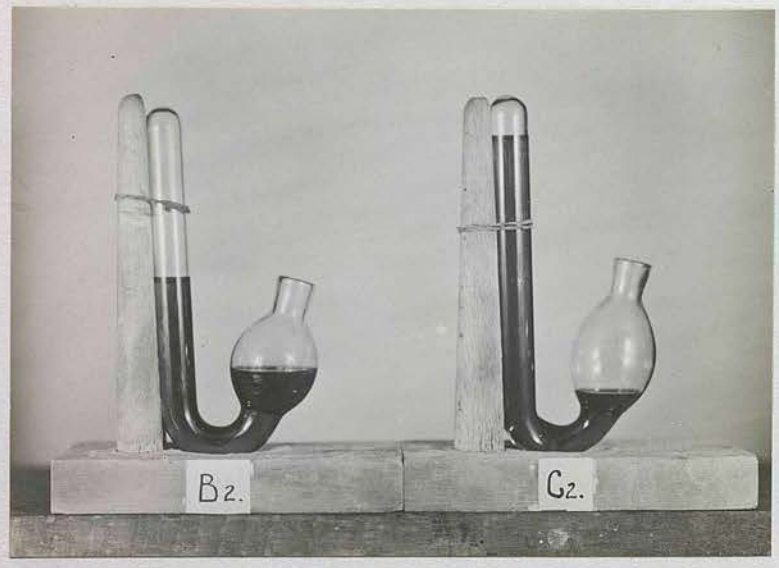
In the earliest stage of impaired function the maximum ability to concentrate fell to circa 3%, but this was unattended by either increase in amount of water excreted or by raising of the minimum concentration. The only change associated with this fall in maximum consisted of a greater concentration of urea in the urine voided during the first hour after the administration of the 2 pints of fluids (Specimen C1) (Stage 1, or early chronic interstitial nephritis).

As renal impairment increased the maximum concentration/

THE UREA CONCENTRATION RANGE.

Definite chronic interstitial nephritis.

Fig. 40.

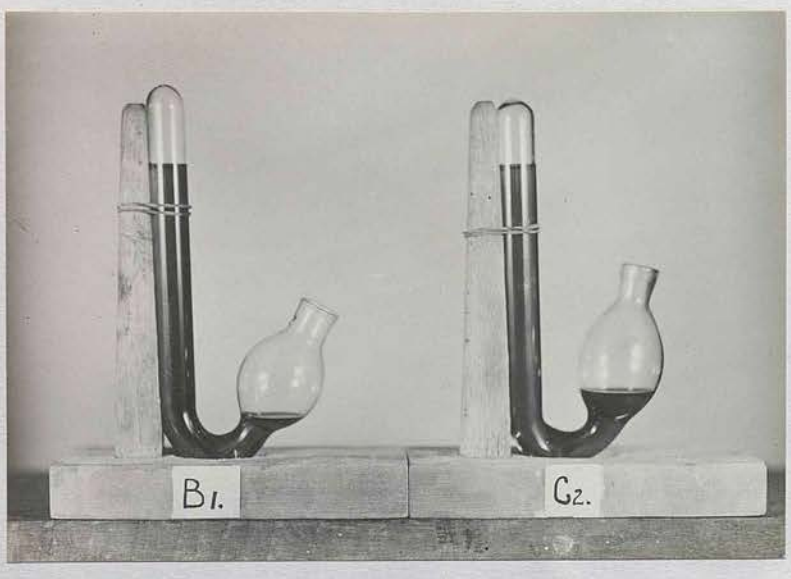


Mrs. C.
Urea concentration range:
Maximum, 2%; minimum, 0.6%.

THE UREA CONCENTRATION RANGE.

Terminal chronic interstitial nephritis.

Fig. 41.



Mrs. S.
Urea concentration range:
Maximum, 1.3%; minimum, 1%.

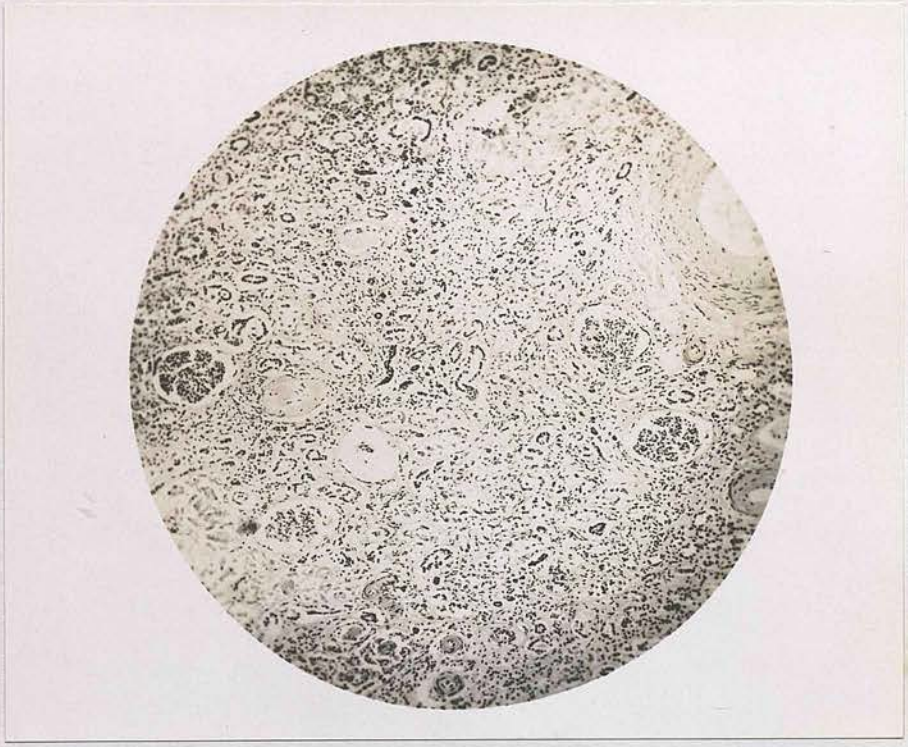


Fig. 42. Mrs. E. (aet.41). Section of kidney shows advanced chronic interstitial nephritis (x 56). Blood urea, 162 mgms. per cent. Urea Range, 1.3%-0.8%. Death from uraemia.

concentration fell to 2.5%. This was accompanied by an increase in the amount of urine passed during the 8 hours' period (Specimens B1 and B2), and by means of this increased output of water the urea given was got rid of, so that in most cases no rise in the minimum was found (Stage 2, or moderate chronic interstitial nephritis).

With still further impairment the maximum was found to fall to 2%. This was accompanied by both an increase in the amount of water excreted during the night (Specimens B1 and B2) and by a rise in the minimum concentration (Stage 3, or definite chronic interstitial nephritis). (Fig. 40).

The further impairment proceeded the lower the maximum fell and the higher the minimum rose. In the fourth stage, or advanced chronic interstitial nephritis, the maximum fell to 1.5%, the associated minimum being 0.85%, while in the terminal Stage 5, a maximum concentration of below 1.5% was associated with a rise of the minimum to 1% or over. (Fig. 41.). (Fig. 42).

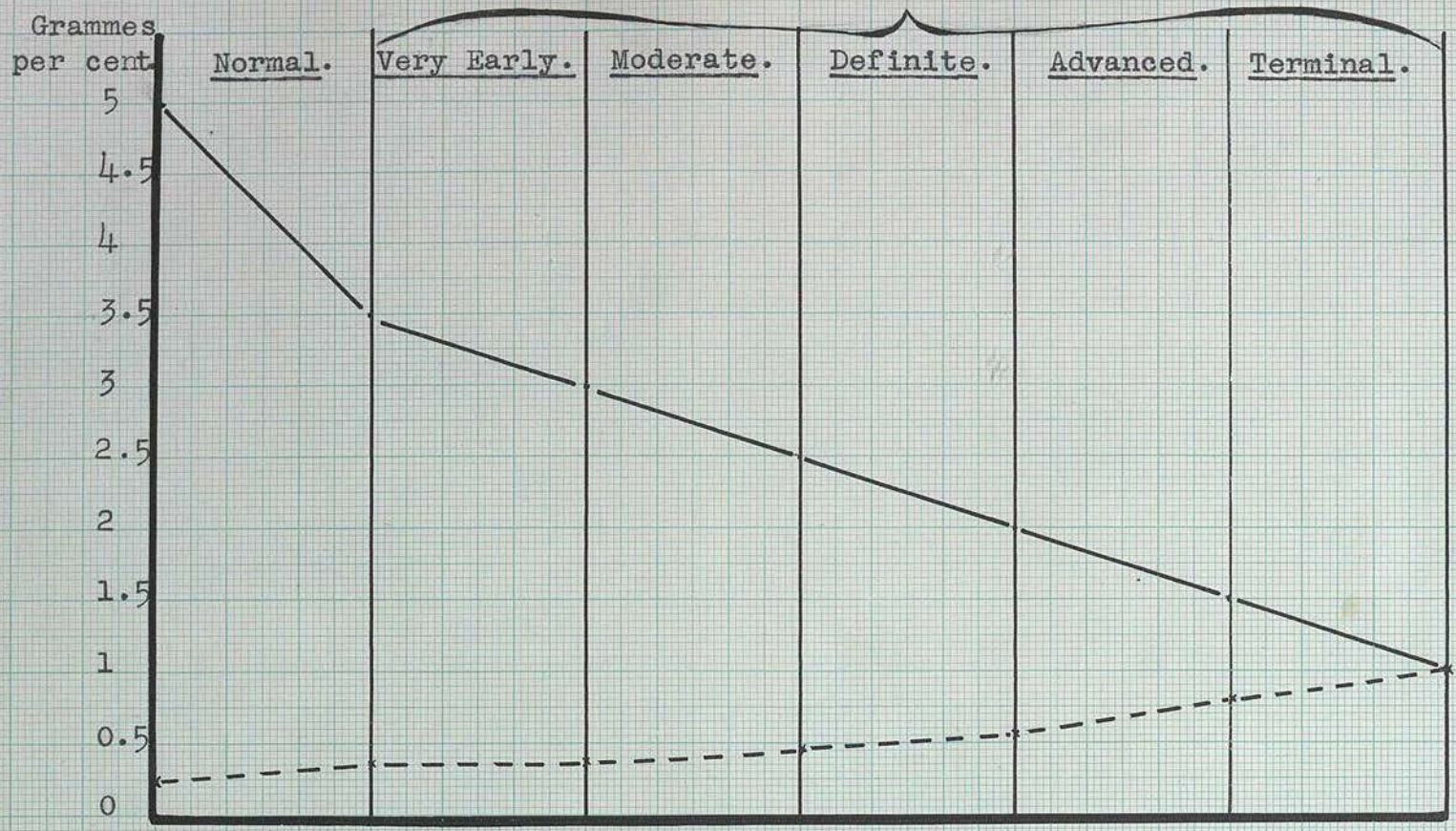
Significance of amounts of urine passed.

It was also noted that in cases in which concentration power was impaired the characteristic water test response was obtained following the administration of/

CHART I

THE UREA CONCENTRATION RANGE.

Chronic Interstitial Nephritis.

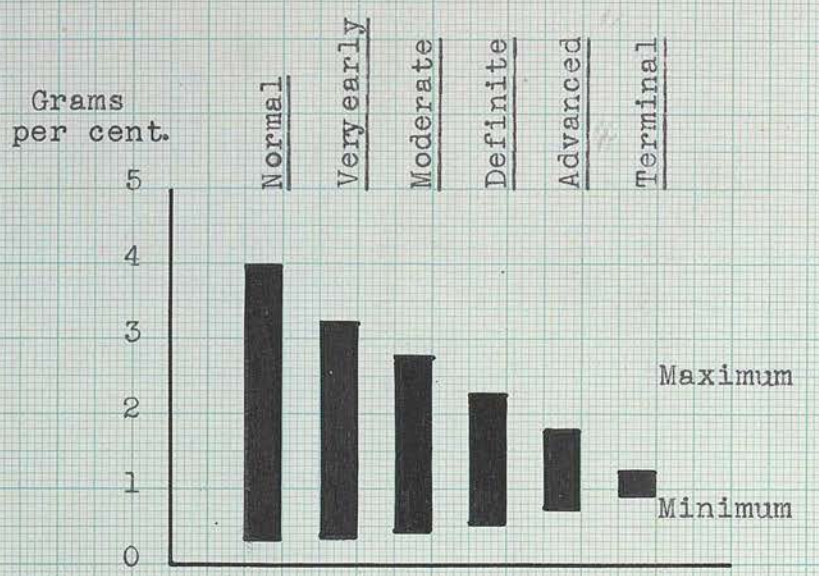


Limiting Values in Normal Individuals and in Various Stages of Chronic Interstitial Nephritis.

Solid line - maximum; dotted line - minimum.

CHART II

THE UREA CONCENTRATION RANGE.



Average values in normal individuals and in various stages of chronic interstitial nephritis, showing maximum and minimum values.

of the fluids. With a rise in the minimum there was an associated inability to cope with the amount of fluid given and the resultant diuresis was delayed beyond normal limits. In the most advanced cases the fluid was very gradually eliminated. It is of interest to note that this response was only obtained in the advanced and terminal cases (Stages 4 and 5). This would suggest that the water test, in contrast to the urea range, is a test for advanced cases of chronic interstitial nephritis only, and is not likely to prove helpful in the doubtful cases where assistance is most required. The importance of the urea range for distinguishing these stages of chronic interstitial nephritis is further discussed in the section dealing with the value of the test in prognosis. Chart I indicates the limits of variations which are allowed in the above stages of renal impairment while Chart II gives the average findings in them.

BLOOD UREA CONCENTRATION IN ASSOCIATION WITH MINIMUM CONCENTRATION IN URINE.

Blood urea concentration was estimated in all cases on completion of the urea concentration range. It was found that in no case with a normal minimum was blood urea/

urea concentration increased. The rise in blood urea in inefficient cases was roughly parallel with the rise of the minimum concentration ability. It would thus seem that the information to be derived from these two is similar and that in a case with a normal minimum no further information will be got from estimation of blood urea. And, of the two, the urinary estimation is by far the simpler. As no change occurs in the blood urea until a heightening of the minimum is present, its estimation will be seen to be of no value in diagnosing those early degrees of the condition (Stages 1 and 2) and also many of the more advanced cases (Stage 3). The value of the test in the differential diagnosis of these two types of high blood pressure is perhaps best appreciated by reference to a few characteristic cases:-

Mrs. A. (aet.67). Florid bullocky type. Blood pressure on admission 250/160; apex beat 6th interspace in nipple line. Blood urea 43 mgms. per cent. Blood creatinine 3 mgms. per cent. Urine - average daily output 35 ounces, S.G. 1018. No albumin. No casts. Urea concentration range 2 results , maximum 3.8% and 3.8%, minimum 0.4% and 0.35%. Ophthalmoscopic examination - both retinae healthy. Blood pressure prior to discharge 150/90. Diagnosis - hyperpiesis. No renal inefficiency.

M.C. (aet.59). Complaint dizziness and breathlessness. Blood pressure 188/130. Heart - apex beat 5th interspace just outwith nipple line. Urine showed no abnormal constituent. Average daily output 45 ounces, S.G. 1018. Retinae healthy. Urea concentration range, 6.iv.28., maximum 3.2%, minimum 0.45%. Diagnosis - very early chronic interstitial nephritis (Stage 1). Prognosis - good as regards/

regards uraemia. January, 1932, - confined to bed due to cardiac condition, but no oedema present. Blood pressure 210/146. Urea concentration range, maximum 1.7%, minimum 0.7%. Diagnosis - definite chronic interstitial nephritis (Stage 3).

Mrs. C. (aet.40). Complaint - shortness of breath, headaches, giddiness of 3 months' duration. Blood pressure 190/140. Apex beat 6th interspace outwith nipple line. Urine - albumin present .2 gr. per ounce . No casts. Average daily output 30 ounces, S.G. 1016. Blood urea 37 mgms. per cent. Ophthalmoscopic examination - "slight degree of vascular thickening. No haemorrhages; no albuminuric retinitis". Urea range, maximum 2.1%, minimum 0.6%. Diagnosis - definite chronic interstitial nephritis. Prognosis - at present good as regards uraemia.

Mrs. S. (aet.28). One year prior to admission, while 4 months pregnant, lost sight of both eyes temporarily, this continuing until abortion occurred at 6th month. Kept well during succeeding two months, then sickness, headaches and weakness set in. While in ward - average blood pressure 180/115. Apex beat 6th interspace outwith mid-clavicular line. Retinae - albuminuric retinitis. Urine - average daily output 52 ounces, S.G. 1012. Albumin positive. Urea range, maximum 1.4%, minimum .95%. Blood urea 57 mgms. per cent. Diagnosis - advanced chronic interstitial nephritis. Prognosis - bad for uraemia. Patient died at home of uraemia two months later.

It will be noticed that in the cases of Mrs. C. and Mrs. S., a diagnosis of definite and advanced chronic interstitial nephritis respectively was made in the presence of a low blood urea content. It is of interest to note that despite this low blood urea death due to uraemia supervened in the case of Mrs. S. within two months.

A.L./

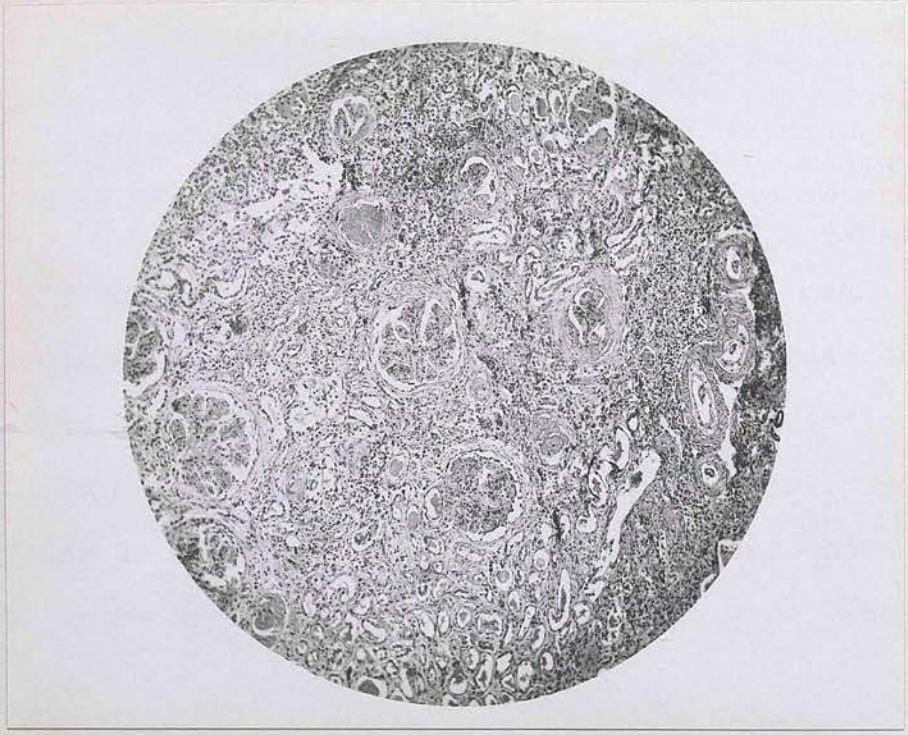


Fig. 43. A.L. (aet.25). Section of kidney (x 52) shows advanced chronic interstitial nephritis. Blood urea, 240 mgms. per cent. Urea Range: Maximum, 1.1%; minimum, 0.8%.

A.L., female (aet.25). Scarlatinal nephritis 5 years prior to admission. While in ward - average blood pressure 185/130. Apex beat 5th interspace in mid-clavicular line. Retinae - haemorrhages and albuminuric retinitis. Urine - average daily output 35 ounces, S.G. 1012. Albumin positive. Urea range, maximum 1.1%, minimum 0.8%. Blood urea 240 mgms. per cent. Diagnosis - terminal chronic interstitial nephritis. Died two weeks later of uraemia. Post mortem - "The appearances are those of the very last stages of a progressive chronic interstitial nephritis" (Fig. 43).

From these cases it will be seen that for the establishment of a diagnosis of high blood pressure definitely not due to chronic interstitial nephritis a normal urea concentration range, at least 3.5%-0.4%, has been deemed a sine qua non. Any fall of the maximum below 3.5% has been looked upon as suggesting the presence of interstitial changes. This may seem unduly harsh, but it has to be remembered that chronic interstitial nephritis is an insidious disease and for years entirely unattended by symptoms and apparent signs. As it is at this early stage that diagnosis is most to be desired it follows that it is in such cases that the ideal renal efficiency test should be applied and interpreted. A renal efficiency test is not necessary for diagnosis at the stage when it can be made from the signs and symptoms. The fallacy of "polyuria and frequency" in these cases is evident from the average daily outputs quoted.

THE UREA CONCENTRATION RANGE AND THE UREA CONCENTRATION TEST.

The average daily needs of the body can be met by an excretion of urea of about 2% concentration. To obtain this it may be necessary to utilise only one third of the kidneys' glomerulotubular systems. Hence it must follow that if the kidney is functioning "all out" following 15 grams of urea a concentration of 2% cannot be regarded as indicative of efficiency. Indeed with the urea concentration range, a maximum ability to concentrate of only 2% evidences a fairly advanced degree of chronic interstitial nephritis. With this as their limit of concentration the kidneys cannot meet the demands placed upon them by the body, and so, unless the diet is restricted with resultant diminution in urea excretion, the blood urea is bound to accumulate rapidly.

It is in this respect that a contrast has to be drawn between the urea concentration range and the urea concentration test of MacLean and de Wesselow. These writers first reported this test in 1918 (151) and in a further communication in the following year MacLean (146, 149) stated that he regarded an ability to concentrate to 2% or over as evidence of efficient kidneys; 1.5%/

1.5% as moderate efficiency; and 1% or less as marked inefficiency. A further communication appeared in 1920(152). It seems obvious, however, that an ability to concentrate to 2% may be sufficient to meet the needs of the body if the whole of both kidneys is continually functioning, yet be actually a sign of inefficiency of the kidneys. With the urea concentration range an ability to concentrate to 2% is evidence of definite functional impairment; at least 3.5% is required to indicate efficient kidneys.

The two tests employ the same amount of urea yet different concentrations are obtained. This difference is due to the times at which the tests are applied. The urea concentration test is applied during waking hours, the urea concentration range during sleep. The greater concentrating power of the kidney during sleep is well known. Hence it is apparent that a test carried out during sleep is more likely to call forth the full action of the kidney than one applied during waking hours. It would thus seem that the urea concentration range has a greater claim than the urea concentration test to be regarded as the ideal renal efficiency test in view of its ability to call forth the full reserve force of the kidneys.

DIAGNOSIS/

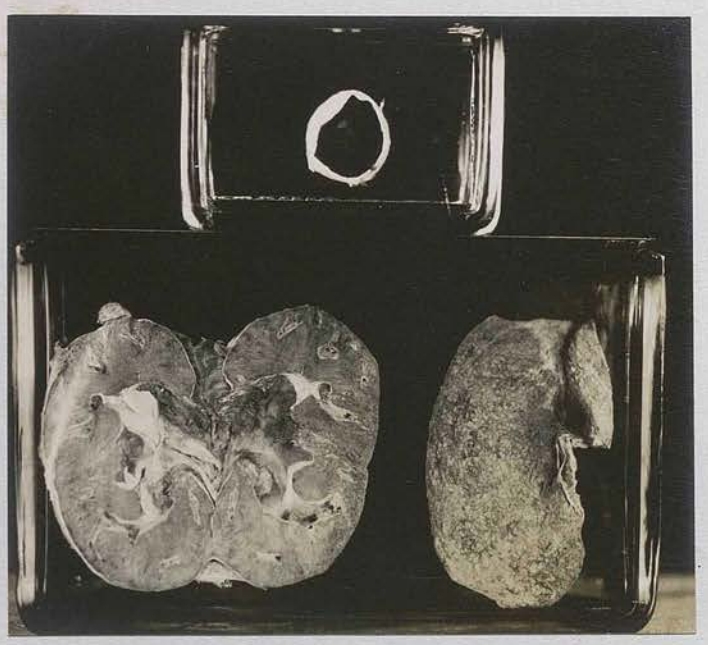


Fig. 44. Mrs.H. (aet.30). Chronic interstitial nephritis with no cardiovascular changes - death from uraemia. (a) kidneys with interstitial changes; and retina with no abnormality.
Urea Range: Maximum, 1.2%; minimum, 0.85%
Blood N.P.N. 114 mgms.%. Average blood pressure 122/78.

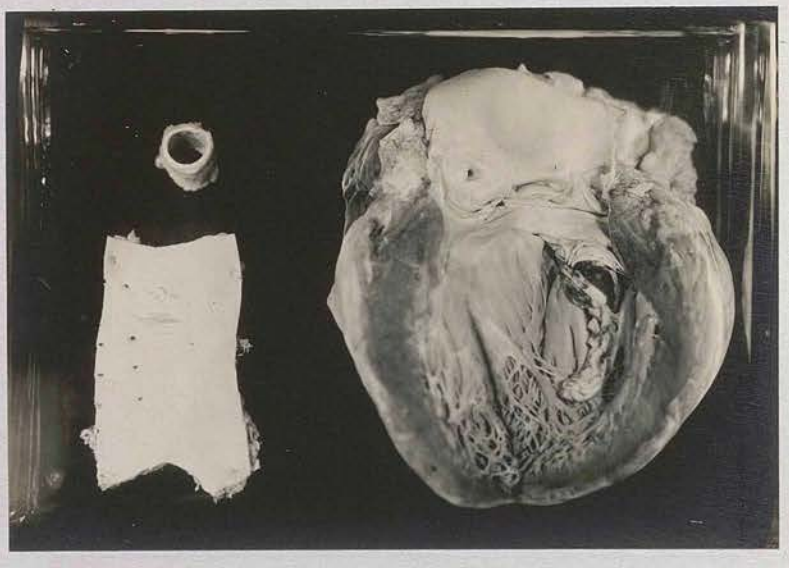


Fig. ##. Mrs.H. (aet.30). Chronic interstitial nephritis with no cardiovascular changes - death from uraemia. (b) heart with no hypertrophy of left ventricle; and portion of aorta and innominate artery showing absence of vascular change. Urea Range: Maximum, 1.2%; minimum, 0.85%. Blood N.P.N. 114 mgms.%. Average blood pressure 122/78.

DIAGNOSIS OF CHRONIC INTERSTITIAL NEPHRITIS WITH NO CARDIOVASCULAR CHANGES.

The urea range is also of value in the diagnosis of cases of chronic interstitial nephritis in which no cardiovascular changes are present. The results obtained in these are as in cases of chronic interstitial nephritis with high blood pressure. Such cases are comparatively rare, but two were encountered during the present investigation. In both cases the diagnosis was established by the urea concentration range and verified by post mortem examination. The findings in these two cases were:-

Mrs. H. (aet.30). Admitted with history of 6 weeks' vomiting and headache, intense to begin with but much better on admission. Blood pressure while in ward varied between 135/95 and 90/60. Heart not enlarged. Urine - average daily output 48 ounces, S.G. 1010. Albumin up to 0.6 gr. per ounce. Ophthalmoscopic examination showed healthy retinae. Blood non-protein nitrogen 114 mgms. per cent. Urea range, maximum 1.2%, minimum 0.85%. Diagnosis - terminal chronic interstitial nephritis. Died of uraemia 5 weeks after admission with cardiovascular findings all normal. Post mortem examination showed small granular kidneys of chronic interstitial nephritis; heart and blood vessels healthy, no retinal changes (see fig.44a,b).

R.T., male (aet.35). Admitted with diagnosis "pyloric stenosis". Complaining of weekly attacks of vomiting and headaches dated to childhood. Average blood pressure 120/88. Heart - apex beat in 5th interspace and within mid-clavicular line. Retinae healthy. Test meal showed achlorhydria. Urine/

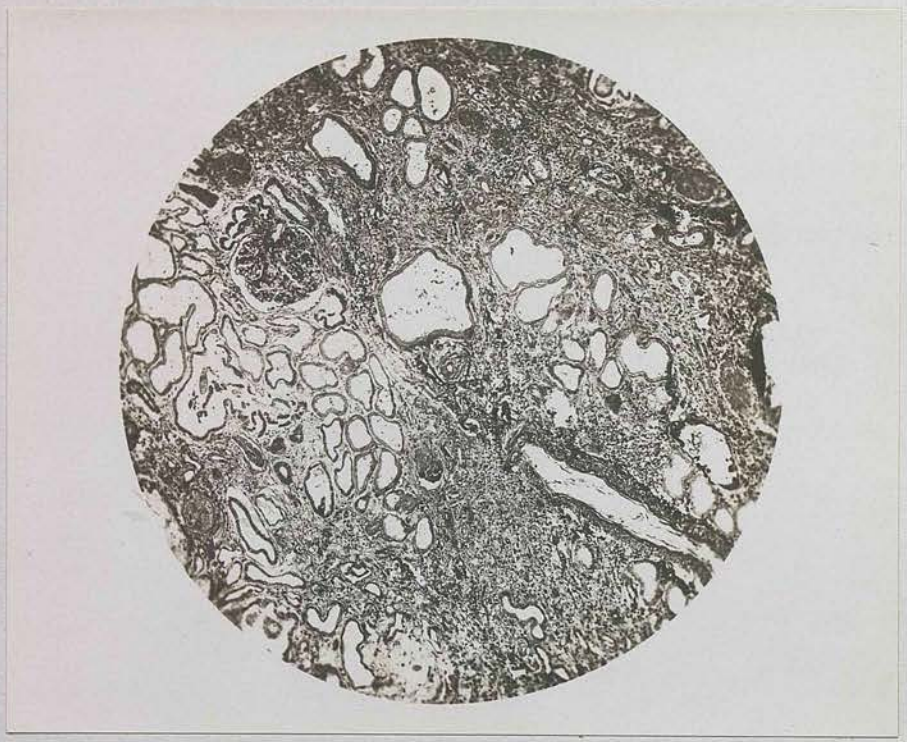


Fig. 45. R.T. (aet.35). Chronic interstitial nephritis. Death from uraemia. Section of kidney (x 56) shows advanced interstitial changes.
Blood pressure: 120/88.
Urea range: Maximum, 1.25%; minimum, 1.2%.

Urine showed albumin but no casts. Urea concentration range, maximum 1.25%, minimum 1.2%. Blood urea 300 mgms. per cent. - done following range findings. Diagnosis - terminal chronic interstitial nephritis with no cardiovascular change. One week later uraemia led to death. Post mortem report - "Micro-examination of both kidneys showed a very advanced chronic interstitial type of nephritis with a slight chronic parenchymatous change". No gastric lesion was found (fig. 45).

In both of these cases the urea concentration range was the definite factor in the establishment of the diagnosis. In the case of Mrs. H. the presence of the comparatively large amount of albumin suggested a parenchymatous lesion but this was negatived by the advanced urea range findings. In the case of R.T. chronic interstitial nephritis was not suspected until the urea concentration range was done two days after admission. The highest blood pressure observed in the two cases was 135/95 in the case of Mrs. H.

POSSIBLE ERRORS IN DIAGNOSIS OF CHRONIC INTERSTITIAL NEPHRITIS BY UREA RANGE RESULT.

A. Prostatic disease.

In the interpretation of the results in suspected cases, two pitfalls have to be avoided. In the male enlargement of the prostate with resultant urinary obstruction/

obstruction leads to a fall in the maximum ability to concentrate urea, while, due to the concomitant rise in blood urea the minimum is also increased, but not to the extent obtaining in chronic interstitial nephritis. The error, however, can be avoided by the correlation of the result with those obtained upon a full examination of the patient, paying particular attention to history, prostatic examination, urinary examination for casts, and cardiovascular examination with especial reference to diastolic blood pressure, and ophthalmoscopic examination. In these cases operative treatment leads to an improvement in urea range findings. It is suggested that the test would prove of value in the preoperative investigation of all prostate cases. The following two cases are illustrative of the above points:-

W.R. (aet.59). Admitted from surgical ward with cancer of prostate and urinary obstruction. Presence of uraemic breathlessness contraindicated operation. Blood urea 58 mgms. per cent. Blood creatinine 2.7 mgms. per cent. Blood pressure 140/80. No abnormality in heart or retinae. Urea range, maximum 1.1%, minimum 0.45%. Post mortem examination revealed cancer of prostate and bilateral pyonephrosis.

J.R. (aet.52). Passing blood in urine. No casts. Albumin not greater than accountable for by blood. Prostate hypertrophied and soft. Blood urea 64 mgms. per cent. Urea range, maximum 1.75%, minimum 0.65%. Prostate removed surgically, following which urea range showed maximum 2.8%, minimum 0.55%, when discharged from hospital.

B./

B. Cardiac failure with oedema.

Cardiac failure with oedema also leads to a urea range which to some extent resembles that of chronic interstitial nephritis in a comparatively early stage. Due probably to the difficulties under which they are working, the kidneys in this condition are unable to concentrate urea to the normal extent and so a maximum concentration of around 2.5% is characteristic being associated with only slight increase in the minimum. As the cardiac failure decreases, the urea range improves as would be expected. The clinical findings naturally prevent the above results being misinterpreted, but difficulty is experienced when the cardiac failure is consequent upon a raised blood pressure. In these cases the only possible procedure is to repeat the range on disappearance of the cardiac failure, following which an assessment of the renal efficiency can be made. Two typical cases are appended for illustration.

J.L., male (aet.30). Mitral stenosis; chronic bronchitis and emphysema. 20.vi.27. Oedema present; urea concentration range, maximum 1.8%, minimum 0.3%. 11.vii.27. Discharged from hospital; breathlessness present but no oedema, and urea range maximum 2.9%, minimum 0.3%. 8.iii.28. Death. Post mortem "Chronic endocarditis of mitral valve with stenosis. Chronic venous congestion of organs. Ascites and oedema". No change found in kidneys other than "those of chronic venous congestion".

Mrs. C./

Mrs. C. (aet.39). Mitral stenosis with auricular fibrillation. Urea range when oedema present, maximum 2.7%, minimum 0.5%. One month later when no signs of cardiac failure, maximum 3.3%, minimum 0.3%.

DIFFERENTIAL DIAGNOSIS OF "HAEMATURIA" OF NEPHRITIC AND NON-NEPHRITIC ORIGIN.

In the differential diagnosis of doubtful acute parenchymatous nephritis and haematuria the urea range may also prove of value. In the former in its early stages there is very marked inability to deal with urea and consequently the characteristic range shows a maximum concentration of around 0.9% and a minimum concentration of about 0.65% - this minimum varying with blood urea. Improvement in the condition shows by widening of the range, but if any degree of acute parenchymatous nephritis be present some impairment of the range will be found. In all the cases of haematuria of non-nephritic origin the urea range was found to be normal. These cases included renal tuberculosis, renal calculus, oxaluria, and one case in which a unilateral double ureter was present, and bleeding was believed to be originating from the crossing of these two ureters. It is not, of course, suggested/

suggested that the urea range should be used as a diagnostic in all cases of acute parenchymatous nephritis. In most it is unnecessary. In the few doubtful cases, however, it may prove of help. Such cases are those described by Beaumont and Dodds (88) and others as focal glomerulo-nephritis in which "haematuria" is the only feature, no oedema or azotaemic symptoms being present. Such slight cases of acute nephritis are frequently misdiagnosed and form possible starting points of so-called "primary chronic parenchymatous nephritis". The great help of the test in the acute cases comes later in the condition and will be referred to under prognosis and treatment.

E.M., female, (aet.28). Complaint - blood in urine. Urine showed blood +, albumin +, no casts and no organisms. Urea concentration range, maximum 3.8%, minimum 0.4%. Diagnosis - non-nephritic haematuria. Cystoscope and pyelography showed double pelvis and ureters on right side, and bleeding coming from lower of these.

A.P., female (aet.22). Complaint - passing blood in urine. Urine showed blood +, albumin trace, no casts and no organisms. Guinea-pig inoculated with urine showed no tubercular lesion. Urea concentration range, maximum 3.5%, minimum 0.3%. Diagnosis - non-nephritic haematuria. Cystoscopy and pyelography showed the haemorrhage to be from the right kidney but no cause was ascertained, "essential haematuria" being diagnosed by exclusion.

W.McI., male (aet.28). Ill for 6 weeks previous to admission with "influenza". Then suddenly became blind, this being accompanied by drowsiness and intense headaches. On admission urine showed trace of/

of albumin and few blood corpuscles microscopically but no casts. No oedema present. Blood pressure 140/90. Retinae healthy. Blood urea 35 mgms. per cent. Urea range, maximum 2%, minimum 0.65%. History and urea range suggested renal inefficiency probably due to acute parenchymatous nephritis. Treated accordingly. This was justified by the later finding of a few epithelial and blood casts in the urine and the improvement of the urea range findings.

ACUTE PARENCHYMATOUS NEPHRITIS AS EXACERBATION OF CHRONIC NEPHRITIS.

Acute parenchymatous nephritis was also frequently encountered as an exacerbation in cases of chronic interstitial nephritis. In these cases the range findings of chronic interstitial nephritis were temporarily superseded by those of the acute condition. Misdiagnosis, however, was prevented by the examination for granular casts, retinal changes and hypertrophy of the left ventricle. As the acute condition cleared up the typical interstitial range findings returned.

CHRONIC PARENCHYMATOUS NEPHRITIS, NEPHROSIS, AND "MIXED" NEPHRITIS.

In chronic parenchymatous nephritis no help can be looked for from the range in making the diagnosis.

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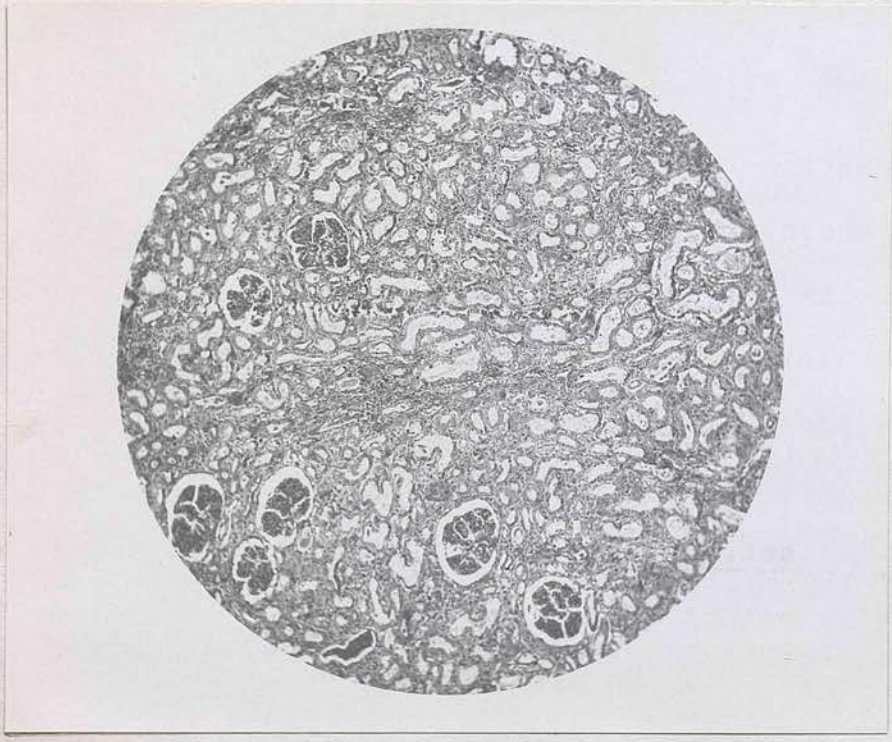


Fig. 46. G.B. (aet.55). Section of kidney shows chronic parenchymatous nephritis (x 56). Blood urea, 37 mgms. per cent. Urea Concentration Range: 3.4% - 0.4%.

In these cases, however, it can be shown that there is no marked impaired ability to deal with urea, as in all cases of this condition the range was found to be either normal or that of only mild interstitial change. One such case came to post mortem examination, and it is interesting to note the range findings in conjunction with those of the autopsy in view of the previous diagnosis, by another ward, of chronic interstitial nephritis. This misdiagnosis may have been due to dependence upon "polyuria and nocturnal frequency" both present in this case.

G.B. (aet.55). Admitted from another ward as case of chronic interstitial nephritis. Urine - average daily output 24 ounces, S.G. 1024. Albumin up to 4.375 grs. per ounce. Granular casts. Blood pressure 138/85. No cardiac hypertrophy. Urea concentration range, maximum 3.4%, minimum 0.4%. Died of generalised anasarca and cardiac failure. Post mortem - chronic parenchymatous nephritis. Section of kidney reproduced in fig. 46 .

J.W. (aet.46). Complaint - "swelling, headaches and breathlessness". Urine - average daily output 65 ounces, S.G. 1016. Albumin up to 5 grs. per ounce. Granular and hyaline casts. Blood pressure 118/80. Heart normal. Urea range showed normal findings with maximum concentration of 3.5%. Three years later re-examination showed urea range maximum 3.4%, minimum 0.45%.

Much similar results were obtained in the one case of primary nephrosis which was examined. In it the urea range was normal maximum 4%, minimum 0.4%.. It will/

will be of interest to note the later change if any in this case in view of the opinion expressed by Shapiro(185)that the ultimate and early fate of all nephroses is chronic interstitial nephritis.

In several cases a mixed chronic nephritis was present, the chronic parenchymatous and interstitial characteristics being both present. In these cases the urea range findings were naturally those of the interstitial variety and so call for no further comment.

A.T., male (aet.24). Complaint - severe headaches, breathlessness, swelling of ankles. Urine - average daily amount varied from 20 ounces on admission to 76 ounces when oedema was going. Albumin 2.5 grs. per ounce. Granular casts. Cardiovascular system: apex beat 6th space 4 inches from mid line. Blood pressure 240/160. Oedema of renal type. Blood urea 73 mgms. per cent. Urea range, maximum 1.45%, minimum 1%. Diagnosis - advanced chronic interstitial nephritis and chronic parenchymatous nephritis.

CONGENITAL CYSTIC KIDNEY.

In congenital cystic kidney it is of interest to note that the findings were typically those of chronic interstitial nephritis. Such is to be expected in view of the changes which are usually present in the functional renal tissue.

T.P., male (aet.43). Complaint- tiredness and pain in right side. Duration 10 months. Both kidneys palpably enlarged. Urine showed albumin in small amount. No casts seen. Average daily output 38/

38 ounces, S.G. 1011. Apex beat in 5th interspace just internal to mid-clavicular line. Blood pressure 170/130. Urea concentration range, 1.3%-0.7%. Cystoscopy and pyelography showed "typical congenital cystic disease". Urea range suggested uraemia as a probable early termination. He died two months after discharge from the ward.

A second case of this kind was followed over a fairly long period and the progress downhill gauged by the series of urea range results. This case is dealt with in detail when the value of the test in prognosis is considered (see case of K.M., page 118).

ORTHOSTATIC ALBUMINURIA.

This condition frequently offers much difficulty in insurance examinations. Is its presence consequent upon a nephritic lesion? Several such cases were examined by means of the urea concentration range and in all of them the results were found to be normal. It can thus be presumed that in these cases there is no impaired ability to excrete nitrogen and that, whatever else may be considered, nephritis of an acute parenchymatous or chronic interstitial type is definitely not present.

P.G., male (aet.18). Height 6 feet. Weight 9 stone 9 lbs. Flat chested. Moro's test +ve. Morning urine albumin -ve. Noon urine albumin +ve when/

TABLE IV showing average urea concentration ranges for different conditions.

Condition	Average maximum	Average minimum
Normal	3.5-4.0%	0.4%
Hyperpiesis	3.5-4.0%	0.4%
Chronic interstitial nephritis		
Very early	3%	0.4%
Moderate	2.5%	0.45%
Definite	2.0%	0.5-0.6%
Advanced	1.7%	0.8-0.9%
Terminal	1.3-1.5%	0.9-1.2%
Congenital cystic kidney - as for chronic interstitial nephritis		
Acute parenchymatous nephritis		
Acute stage	0.9%	0.65%
Recovery	at least 3.5%	0.4%
Haematuria	3.75%	0.4%
Orthostatic albuminuria	3.6%	0.3%
Chronic parenchymatous nephritis	3.2%	0.4%
Nephrosis	4.0%	0.4%
Cardiac failure	2.5%	0.5%
Prostatic obstruction	1.7%	0.7%
Other urinary conditions	3.5-4.0%	0.4%

when up. No blood or casts. No oedema. Urea concentration range, maximum 3.6%, minimum 0.3%.

D.C., male (aet.16). Height 5 feet 9 inches. Weight 7 stone 10 lbs. Urine showed albumin when up, but this disappeared on confinement to bed. No blood or casts. Urea concentration range 3.5%-0.3%.

OTHER URINARY CONDITIONS.

The test was also applied in other conditions affecting the urinary tract, but in these normal findings only were obtained. This series included cystitis, pyelitis, pyelo-nephrosis, and hydronephrosis.

J.W.W., male (aet.26). Complaint - frequency of micturition. Urine showed no abnormality. Blood urea 40 mgms. per cent. Blood pressure 126/72. Urea concentration range, maximum 4%, minimum 0.2%. Cystoscopic examination: small ulcers on left side of bladder. ?Tubercular. No tubercle bacilli found in urine. Moro's test negative.

The value of the test in diagnosis can best be summarised in tabular form (see Table IV). Reference to this table will show that the range shows impairment in conditions in which ability of the kidney to excrete nitrogenous waste is present - chronic interstitial nephritis, congenital cystic kidney, enlarged prostate with obstructive changes, and cardiac failure with oedema; while no departure from normal limits is found in primary hyperpiesis including arteriosclerosis, chronic parenchymatous nephritis, nephrosis, haematuria, orthostatic/

orthostatic albuminuria and conditions affecting parts of the urinary tract other than the kidney.

Its outstanding use in diagnosis is in distinguishing between cases of high blood pressure due to chronic interstitial nephritis and those in which no renal change is present. It is capable of showing such renal involvement in its very earliest stages, and as it is in these stages that a definite diagnosis is most to be desired, the test will be of evident value for this purpose alone. Any impairment of range, however slight, should lead to suspicion, and repetition at intervals to enable a clear picture to be obtained. Other tests show the presence of renal damage at a comparatively advanced stage; with the urea range renal impairment can be demonstrated at its commencement.

VALUE OF UREA CONCENTRATION RANGE IN PROGNOSIS.

The renal efficiency tests are usually regarded solely as diagnostic aids. Beaumont and Dodds express the opinion "that renal function tests, considered from the medical aspect, fall short in the fact that they do not provide a diagnosis, and give a poor idea/

idea as to prognosis". The urea concentration range serves a useful purpose in prognosis.

Prognosis in chronic interstitial nephritis.

In high blood pressure with no renal lesion, the dangers are those of haemorrhage especially cerebral, cardiac failure, and intercurrent disease, in this order of frequency. As the normal urea concentration shows, there is no danger of uraemia. In chronic interstitial nephritis, cerebral haemorrhage and cardiac failure are grave dangers due to the high blood pressure, but ranking along with these in importance is the possibility of uraemia due to the renal defect. In prognosis the height of the diastolic blood pressure, the frequency of the heart rate, and the presence or absence of extra systoles are helpful in the first two possibilities; in prognosing the probability of uraemia the urea concentration range is of very distinct help.

As the degree of chronic interstitial nephritis increases, the urea concentration range decreases. In the early stages a maximum of over 2% indicates that uraemia is not likely; when below 2% uraemia is to be expected within a year, if the circulatory dangers do not/

not previously intervene. A maximum of below 1.5% with a minimum rising towards 1% is indicative of an early termination from uraemia. Urea is accepted as definitely not the cause of uraemia, but the ability of the kidney to excrete it forms the best indication of the probability of its onset. This ability is very definitely indicated by the urea concentration range.

Illustrative cases.

Mrs. N. (aet.53). Complaint - nervousness, palpitation and vomiting. Blood pressure varied from 270/210 to 210/168. Heart, apex beat 6th interspace one inch outside mid-clavicular line. Retinae - "oedema of discs: arteriosclerotic changes: and few small haemorrhages". Urine - average daily output 36 ounces, S.G. 1010. Albumin 2.6 grs. per ounce. Urea concentration range, maximum 1.45%, minimum 0.8%. Blood urea 107 mgms. per cent. Blood creatinine 2.3 mgms. per cent. Diagnosis - terminal chronic interstitial nephritis. Died of uraemia 3 weeks later. Post mortem examination showed very advanced chronic interstitial nephritis.

T.C., male (aet.34). Complaint - breathlessness and vomiting. Blood pressure 200/140. Apex beat 6th interspace in mid-clavicular line. Retinae showed "oedema of upper inner quadrants of both discs with one or two flame-shaped haemorrhages. No exudate". Urine - average daily output 85 ounces, S.G. 1010. Albumin and trace of blood present. Microscopic examination showed blood, epithelial and granular casts. Urea concentration range, maximum 0.75%, minimum 0.6%. Blood urea 146 mgms. per cent. Diagnosis - terminal chronic interstitial nephritis with acute acerbation. Died of uraemia 4 months later. Post mortem report - "small red granular contracted kidney of advanced chronic interstitial nephritis".

In the above two cases it is of interest to note

that/

that though both patients died of uraemia due to chronic interstitial nephritis the characteristic retinal changes associated therewith were found in neither case.

Value in following progress of condition.

With the range the progress of the condition can be easily followed. Hence it is imperative that it be repeated at intervals in all cases of renal impairment, so that a new evaluation of the degree of inefficiency may be arrived at. This procedure has been adopted in all cases in this series which were under observation for a sufficiently long period, or which returned to the wards. By its aid, it was possible to follow the downhill course which such cases pursue. The following case, in which the urea range findings were confirmed by post mortem examination, illustrates the value of this procedure.

K.M., female (aet.40). Admission to the ward was first due to haematemesis resultant from a gastric ulcer. The urea range was applied on that occasion in consequence of a high blood pressure and renal impairment was thereby detected and assessed. A second admission 6 months later showed increased renal impairment; 3 months later this was very advanced and signs of uraemia were present. Perforation of the gastric ulcer then occurred, operation was performed under spinal anaesthesia but death resulted from uraemia six days later. At the post mortem examination bilateral congenital cystic kidney was found and microscopic examination showed advanced interstitial changes in the renal tissue/

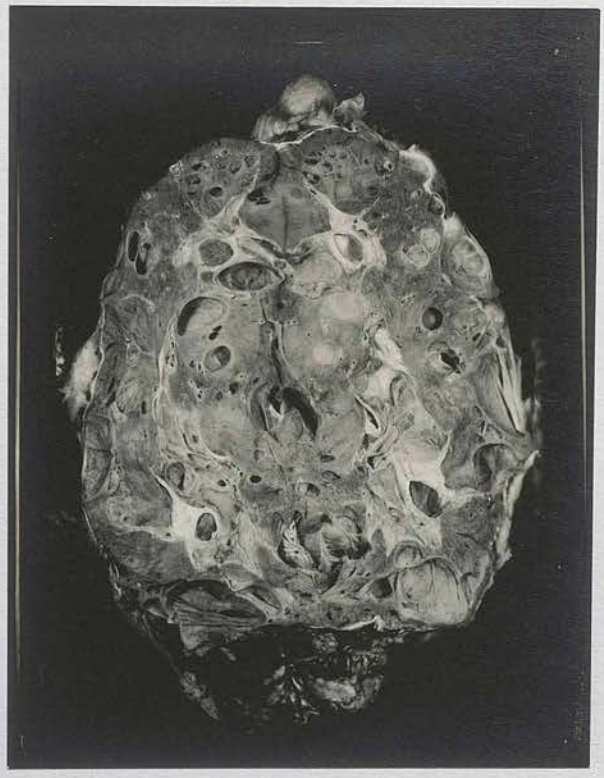


Fig. 47. K.M. (aet.40). Congenital cystic kidney. Details of series of urea ranges etc. given in text.

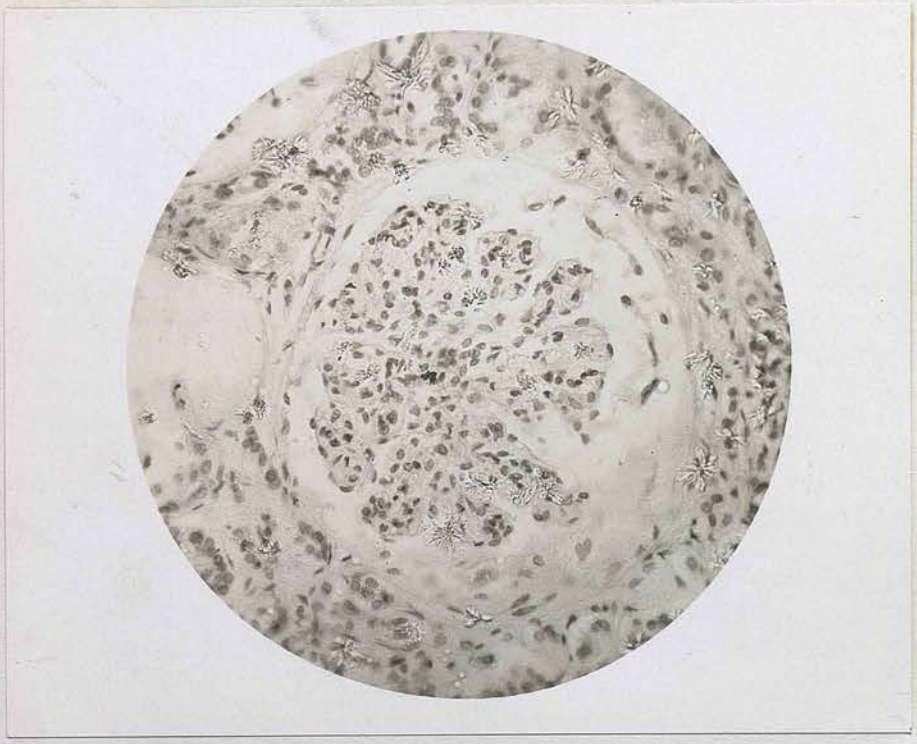


Fig. 48 . K.M. (aet.40). Congenital cystic kidney. Section of kidney (xanthhydrol method) shows interstitial changes in kidney tissue and dixanthyl urea crystals in glomerular capsule and interstitial tissue. (x 260)

tissue (figs. 47, 48). The downhill progress of this case can be followed best by reference to the urea range findings.

		Maximum	Minimum
12.9.29.		2.3%	.45%
7.3.30.		1.7%	.5%
15.4.30.		1.5%	.55%
27.7.30.		1.1%	.9%
26.8.30.	Death.	Post mortem - congenital cystic kidneys.	

This case, in addition to illustrating the course of such cases, also bears out the observations made on the value of the test in prognosing the onset of uraemia. On her first admission the maximum concentration of 2.3% suggested uraemia as a possible termination in 12 months' time if the cardiovascular terminations did not previously intervene. Six months later the range showed uraemia to be fairly imminent and the last range done 13 days prior to perforation showed the outlook to be a matter of days. It can safely be asserted that the operation in no way hastened the end, as she was in uraemia before this occurred; indeed she seemed to improve in this respect for the first 2 days following the operation.

Prognosis in acute parenchymatous nephritis.

MacLean (150) illustrates the prognosis in acute parenchymatous nephritis:

Acute stage:
- Azotaemic type with N_2 retention, etc. → Represents interstitial type of chronic Bright's
- Hydraemic type with oedema → Represents parenchymatous type of chronic Bright's
- Either type → Recovery.

The progress to chronic parenchymatous nephritis is doubtless the commoner and also the easier to observe in view of the persistence of the urinary albumin and the/

the oedema. Hence probably the care directed towards this and the scant attention paid to the possibility of azotaemic tendency. The degree of interstitial damage, however, can be ascertained by repeated urea range examination. In the early acute stages the characteristic result shows a maximum of about 0.9% and a minimum of about 0.6%. As improvement takes place the return of the range towards normal can be observed, and, if treatment be persevered with patiently, the full normal range will eventually be obtained. No case of acute parenchymatous nephritis should be considered cured until the urea concentration range returns to a full normal. Too often the disappearance of albumin leads to the discharge of the case; as often the azotaemic element is forgotten despite its even greater importance. The urea range, however, offers an easy means of following the recovery of this function and should be applied repeatedly as a routine before an acute parenchymatous nephritis case is discharged from treatment.

Illustrative cases.

In these cases the urea concentration range was not applied in the early stage as it was unnecessary for diagnosis. This procedure was followed in all frank cases, the test only being utilised in the later stages/

stages to assess the degree of azotaemic recovery.

K.M., female (aet.16). 24.ix.30. Admitted with oedema; urine showing albumin, blood, and blood and epithelial casts. 11.x.30. Urine free of albumin, blood and casts. Urea range, maximum 2.6% minimum, 0.35%. 1.xi.30. Urea range, maximum 3.05% minimum 0.3%. 5.xi.30. Urea range, maximum 3,15%, minimum 0.3%. Following this discharged home for domestic reasons against advice as urea range not yet returned to normal.

E.W., male (aet.8). 25.xi.31. Admitted with oedema; urine showing albumin 0.87 grs. per ounce; blood; and blood and epithelial casts. History of tonsillectomy 8 days prior to admission. 1.xii.31. Blood urea 34 mgms. per cent. Urine showing blood and albumin. 16.xii.31. No blood in urine; faint trace of albumin. Urea range, maximum, 3.2%, minimum 0.45%. 21.xii.31. No albumin in urine. 29.xii.31. Urea range, maximum 4.4%, minimum 0.4%. Allowed up. 4.1.32. Discharged home.

C.D., female (aet.25). 15.vii.31. Admitted with oedema of ankles and face of 10 days' duration. Urine - albumin; blood; blood and epithelial casts. Blood pressure 190/120. No history of previous nephritis. 22.vii.31. Urine - albumin 0.8 grs. per ounce; no blood. Blood urea 52 mgms. per cent. cholesterol 115 mgms. per cent. Urea range, maximum 1%, minimum 0.7%. 9.viii.31. Urea range - maximum 1%, minimum 0.6%. Blood pressure 120/80. Ophthalmoscopic examination showed no abnormality. 17.viii.31. Patient worse. Return of oedema. Blood in urine. Blood pressure 140/88. Blood urea 58 mgms. per cent. 18.viii.31. Urea range, maximum 0.75%, minimum 0.6%. 21.ix.31. No change in condition. Plasma proteins-albumin 2.3 grams per cent. globulin 1.6 grams per cent. CO_2 combining power 23 volumes per cent. Blood cholesterol 220 mgms. per cent. 21.x.31. Condition improved. Urea range - maximum 1.6%, minimum 0.6%. 9.xi.31. Improvement maintained. Blood urea 34 mgms. per cent. 23.xii.31. Further return of oedema and blood in urine.. Blood urea 30 mgms. per cent. Blood pressure 200/130. 9.1.32. Condition in statu quo. Urea range maximum 1%, minimum 0.7%. 12.1.32. Urea range maximum 1%, minimum 0.8%. Blood urea 28 mgms. per cent. 22.1.32. Transferred to St. Raphael's Home. 1.11.32. Death from uraemia. No post mortem examination.

In/

In the first of the above cases the urea concentration range showed a return of azotaemic function to what has been called, when dealing with chronic interstitial nephritis, the very early interstitial condition. Doubtless had treatment been persevered with, the condition would have returned to normal as in the second case. As the patient was a seasonal potato worker from Ireland, it has been impossible to follow her, but doubtless she shows some slight impairment of her reserve force, and so has less margin should interstitial nephritis later supervene. In the second the interstitial tissue can safely be assumed to have returned to normal, and so in his case complete recovery has taken place as the hydraemic evidences are also absent. Case 3 typifies the other class which fails to clear up. To begin with progress was satisfactory, and the ability to deal with urea was improving when exacerbation led to retrogression. Following this repeated urea ranges showed little indication of satisfactory recovery of azotaemic function. Her condition was consequently regarded as parallel with that of advanced chronic interstitial nephritis the early fatal termination of which due to uraemia was to be expected. This followed within 10 days of discharge from the ward. Thus in the first two cases the urea range evidences a a good prognosis: in the third, the opposite holds.

THE UREA CONCENTRATION RANGE IN TREATMENT.

The urea concentration range can also be used in guiding the treatment of cases showing renal impairment. Of these the chief are acute parenchymatous nephritis, chronic interstitial nephritis (including congenital cystic kidney), chronic parenchymatous nephritis and nephrosis, and cardiac failure with oedema.

Treatment of acute parenchymatous nephritis.

In acute parenchymatous nephritis two main views are held regarding the treatment of the acute stage. Van Noorden (161) regards glucose and fruit juice as the rational diet during this phase, holding that the administration of milk and other proteins imposes an unnecessary burden upon organs which, being inflamed, should be rested as much as possible. Complete rest cannot be attained as urea and other nitrogenous compcompounds are always being formed from tissue breakdown, and these will utilise the available azotaemic excretory power of the kidneys to the full. Consequently he attempts to confine azotaemic excretion to this endogenous nitrogen by excluding all exogenous sources including milk. In this country, on the other hand, milk forms the staple diet during the acute stage, being given at regular intervals in amounts around/

around 2 pints daily. This régime is easily defended as milk provides every essential of a diet and provides them in an easily digested and assimilable form: it is also diuretic in action in this condition. Moreover in caseinogen the body is presented with every amino acid required for tissue synthesis, and as tissue breakdown is continuing during the disease it is but reasonable to allow the materials for replacement. Further, if the amino acids are being utilised for fresh tissue formation they cannot be katabolised to yield urea for the kidneys to excrete. Hence as the "perfect protein food" it seems milk is justifiable during this stage and that no other protein is necessary.

The body, however, only requires a certain amount of protein for tissue synthesis and then utilises the remainder for heat production. As deamination and urea formation must precede heat production from protein, it follows that, besides being a wasteful fuel, protein excess will necessitate kidney action to excrete urea. The reasonable diet in this stage would thus appear to be a combination of the above two principles, utilising milk as the provider of the essential amino acids for tissue synthesis and so maintaining the general condition of the body, and adding glucose and fruit juice as providers/

providers of body heat. With this régime the general condition suffers much less than it does when either of the above two alone is employed, for tissue loss is prevented and yet no extra burden is imposed on the inflamed kidneys. This is shown by the ability of the kidneys to eliminate nitrogenous waste without attaining their limit of ability (this can be ascertained by application of the urea range in the acute stage) and also by the non-accumulation of further urea and other nitrogenous constituents in the blood. A diet suitable for this stage is given in the Appendix.

With the passing of the acute stage it becomes necessary to add to this diet. It is at this point that the urea range offers most help in the treatment of acute parenchymatous nephritis. Protein has to be added and the addition has to be made in some form other than milk, of which most patients very soon tire. Yet in making the addition care has to be taken that the powers of the kidney are not exceeded. For this purpose the repeated application of the urea range is urged. A correct assessment of the functional ability of the kidneys can then be obtained and the diet can be arranged so that the nitrogenous residue will not entail the employment of the whole of this ability. Diets of varying protein content and the urea elimination consequent thereon are further discussed when the treatment/

treatment of chronic interstitial nephritis is dealt with.

When is the acute parenchymatous nephritis patient to be allowed up out of bed? Too often a urine free from albumin is taken as the indication provided the blood condition does not show too great a degree of anaemia. This, however, merely pays regard to one point in the condition. In dealing with cases of lobar pneumonia, it is now generally agreed that the patient should not be allowed up until every physical sign in the lungs, heart and other systems has returned to normal. It is of the utmost importance to employ the same standpoint in treating acute parenchymatous nephritis. No case should be allowed up until all functions of the kidneys have been ascertained to have returned to normal. The urine and blood constituents usually regain normality comparatively soon, yet a urea range applied at this stage will show that the azotaemic function of the kidney is still defective. Until a normal urea range has been obtained, the kidneys cannot be assumed to have regained their full reserve power, and until this full pre-nephritic power of the kidneys has been restored the patient should be confined to bed. Chronic interstitial nephritis is all too prevalent and too serious economically to allow of the/

the possibility of its incidence being increased by faulty and impatient treatment of acute parenchymatous nephritis. One case is quoted to show the recovery of this azotaemic function following the observance of the above treatment during and after the acute stage.

J.C.(aet.13). 8.iv.31. Admitted with oedema; and urine showing albumin 4.5 grains per ounce, blood, and blood and epithelial casts. Blood urea, 70 mgms. per cent. Duration of illness 2 weeks. Treatment instituted with milk, glucose and fruit juice diet. 24.iv.31. Albumin and blood in traces in urine. Blood urea 47 mgms. per cent. 30.v.31. Urine showed small trace of albumin but no blood. Urea concentration, maximum 2.4%, minimum 0.5%. Protein content of diet increased. 1.vii.31. Urine normal. Urea concentration range, maximum 3.3%, minimum 0.4%. 14.vii.31. Urea concentration range, maximum 3.5%, minimum 0.3%. Allowed up and placed on ordinary diet. Transferred following this to Astley Ainslie Institution. On discharge from there, (16.x.31) urea concentration range showed maximum 4.3%, minimum 0.45%.

Treatment of chronic parenchymatous nephritis and nephrosis.

The modern treatment of chronic parenchymatous nephritis and nephrosis as suggested by Epstein (11,12) is now generally accepted. This consists in allowing the patient a diet of high protein content. This provides the patient with abundant albuminous material and at least affords the possibility of increasing his depleted plasma proteins, the diminution in blood osmotic tension consequent upon protein reduction being now fairly generally accepted as the cause of the oedema.

In/

In addition the protein assists in keeping up the patient's general condition. Too often in the past attention has been focussed upon the kidney and the albuminuria, and the general condition has been lost sight of. Now the relative unimportance of the albuminuria and the inability to lessen it by dietetic measures are being realised, and the tendency is to ignore the local condition and regard the general. A third reason advanced for this treatment is that it leads to the production of a large amount of urea and urea is undoubtedly the best diuretic in this condition (MacLean (150)). Ashley Mackintosh (144) and others not only regard this urea formation of importance, but give urea in doses of 50-300 grains thrice daily in addition for its diuretic action.

Before this method of treatment can be adopted, however, it has to be established that the kidneys are capable of dealing with this large amount of urea. For this purpose the urea range should be applied prior to the commencement of treatment and the exact degree of azotaemic function would thus be ascertained. No case with less than 3.5% of a maximum concentration power should be given a high protein diet with urea in addition.

Treatment/

Treatment of cardiac failure.

The treatment of cases of cardiac failure entails similar comment. Bulky carbohydrate meals are forbidden in this condition and substituted by frequent small meals mainly of protein character. This treatment is a suitable one if a reasonable amount of azotaemic function be present in the kidney. In addition, however, urea is frequently employed as the diuretic of choice. In hydraemic cardiac failure the full reserve azotaemic power of the kidney is not present, and the administration of urea may merely mean the placing of an extra burden upon an organ just succeeding in meeting the body's needs. Other diuretics, consequently, should be tried first, and urea only used when these have failed, and when the urea range has demonstrated a sufficiently good azotaemic power to allow for its elimination. As the oedema diminishes the reserve azotaemic power will return and, as this is shown by the urea range, the amount of urea given can be increased.

Treatment of chronic interstitial nephritis.

The diagnosis of chronic interstitial nephritis very frequently leads to an immediate and extreme curtailment of protein intake. As already emphasised, protein is absolutely necessary for the maintenance of/

of the tissues and the general condition. Yet often the curtailment of protein in these cases is so extreme that tissue replacement is not allowed for and the course is more rapidly downhill than it would have been even in a case allowed full ordinary diet. The aim in treatment of chronic interstitial nephritis should be to maintain the general condition by giving as full a protein diet as is consistent with the kidneys' ability to excrete nitrogenous metabolites.

As has been pointed out in the section dealing with the diagnosis of this condition the urea range serves a useful purpose in ascertaining the degree of reduction of azotaemic reserve power of the kidneys. Not only does it show whether the kidneys are efficient or inefficient, but also it gives an accurate indication of the degree of any inefficiency present. This gives the urea range its place in the treatment of chronic interstitial nephritis. The ability of the kidneys to deal with urea should be ascertained at regular intervals by application of the urea range, and the protein content of the diet so regulated as never to employ more than two thirds to three fourths of the kidneys' azotaemic functional power at one time. Thus when the diagnosis is made the patient should be placed on a diet of protein content consistent with his ability to excrete urea. Then at least every three months the range/

range should be repeated, and any alteration in his maximum concentration should lead to a revision of the diet.

Renal requirements of endogenous protein metabolism.

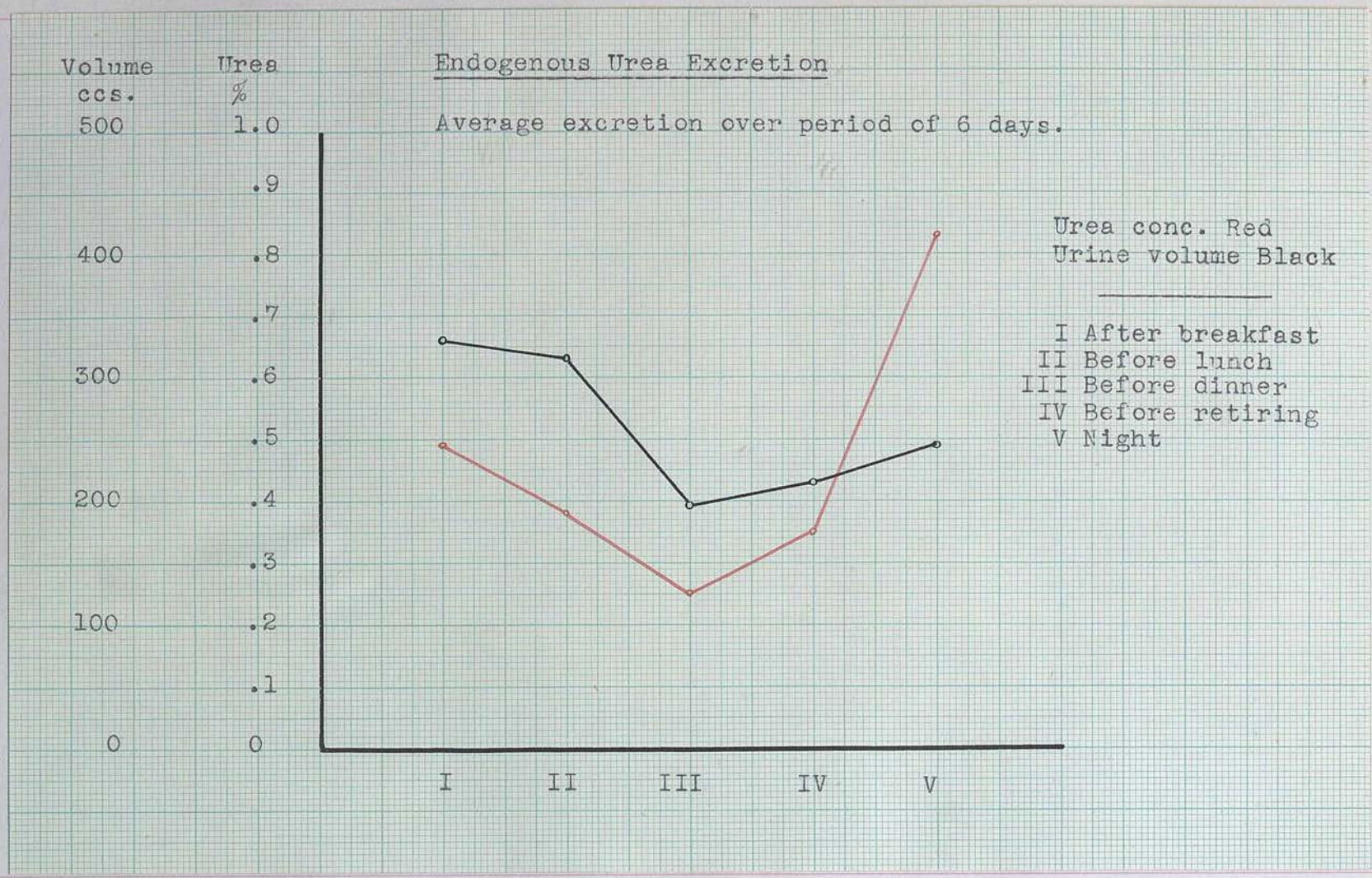
To ascertain the degree of renal activity required to deal with endogenously produced urea only, personal experiments were conducted. As far as could possibly be managed, a protein-free diet was taken over a period of 22 days. During the earlier days of this period the expected variations were met with, but thereafter a fairly constant excretion was obtained. Urine was voided at definite hours, and was examined for urea, total nitrogen, and creatinine content. The total nitrogen content was used merely as a check upon the urea results; the creatinine determinations formed an interesting study in endogenous metabolism. The methods used were the sodium hypobromite method for urea; the incineration, aeration and absorption method (Taylor, 193) for total nitrogen; and Folin's (116) sodium hydroxide and picric acid colorimetric method for creatinine. As the urea results only are concerned with the present study these alone are quoted in the appended table which gives the results over six typical days after equilibrium/

TABLE V.

Endogenous Urea Excretion

Day	After breakfast		Before lunch		Before dinner		Before retiring		Night	
	Amt. ccs.	Conc. %	Amt. ccs.	Conc. %	Amt. ccs.	Conc. %	Amt. ccs.	Conc. %	Amt. ccs.	Conc. %
17th	360	.8	240	.3	240	.3	165	.3	210	1.
18th	300	.5	240	.2	180	.25	420	.15	180	.8
19th	270	.55	240	.5	150	.35	60	.7	240	.9
20th	360	.45	390	.15	-	-	270	.15	245	.9
21st	360	.3	540	.15	180	.15	165	.2	360	.55
22nd	330	.35	240	1.	240	.2	210	.6	240	.85
Average	330	.49	315	.38	198	.25	215	.35	246	.83

CHART III


Volume ccs.
Urea %
500
400
300
200
100
0
1.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
0
I
II
III
IV
V
Endogenous Urea Excretion
Average excretion over period of 6 days.
Urea conc. Red
Urine volume Black
I After breakfast
II Before lunch
III Before dinner
IV Before retiring
V Night

equilibrium was established. Table V and Chart III show that the average 24 hours' output over this period was 1320 ccs. with an average urea concentration of 0.43% giving an average daily output of urea of 5.75 grams. During this period the night concentration always exceeded the day concentration, the highest recorded being 1% by night and .55% by day. The lowest concentration obtained over the period was 0.15%. It will thus be seen that the endogenous urea alone calls for renal efficiency sufficient to allow for an average 24 hours' concentration of 0.43%, while the highest demand it is likely to place upon the kidney is 1%.

The effect of withdrawal of protein upon the general condition can be seen from the loss of weight occasioned by the experiment. During the preliminary part before protein was withdrawn the weight was 10 stone 1 lb. At the end of the experiment this had been reduced to 8 stone 11½ lbs. The ordinary occupation was followed throughout.

The figures obtained during this experiment have to be compared with those given by Samson Wright (209). He states the daily nitrogen excretion during starvation to be 11.4 grams, this being equivalent to a daily urea nitrogen excretion of 9.12 grams assuming 80%/

80% of the total urinary nitrogen to have been derived from urea. These figures are, however, during complete starvation. In the experiment reported here only protein starvation was present, a diet of full calorific content (2600 C) being provided from carbohydrate and fat. Also in protein starvation it is very doubtful if more than 50% of the urinary nitrogen appears as urea. The control non-protein nitrogen estimations carried out in this experiment suggest that 60% is the maximum proportion of urinary nitrogen which can be attributed to urea. The discrepancy between the results obtained in this experiment and those quoted by Wright is probably due to a combination of the above two factors.

The urea excreted during this period must have been endogenously produced from the deamination of amino acids resulting from the breakdown of tissue protein. As far as was possible no amino acid was being ingested and consequently loss of body tissue occurred with resultant loss of weight. Had essential amino acids been added as the only protein to the diet it is conceivable that a certain amount could have been given without leading to any increase in urea output, due to all of these amino acids being utilised for tissue synthesis with consequently no formation of urea/

urea therefrom. It would thus seem possible for protein to be administered in the diet without leading to any increase in the nitrogen excretion; but this protein would require to be all of an essential nature and also require to be in amount just sufficient to cover tissue breakdown. Unfortunately the mixed protein of our diet is not all capable of yielding essential amino acids, and so any protein ingestion is bound to lead to a rise in urea excretion above the basal endogenous level due to the katabolism of the non-essential.

Urea excretion with diets of varying protein content.

With a view to ascertaining the urea elimination following known intakes of general mixed protein the experiment was extended to include patients with normal kidney function (as ascertained by urea range). Diets of varying protein content were given. The urine was passed at definite times and output, urea concentration, and total urea content, were estimated. By this means the variations in urea concentration and excretion at different times of the day were observed and the relationship between these and protein intake noted.

Langdon Brown (95) states 94 grams of protein to be the maximum intake of a chronic nephritic, this being equivalent to an excretion of 15 grams of nitrogen/

nitrogen (or 25.7 grams of urea), while 60 grams of protein plus the amount which is being lost in the urine, is stated to be the minimum. If 25.7 grams of urea have to be excreted and the average daily output is to remain at 1500 ccs. (50 ozs.) there must be an average concentration of urinary urea of 1.71% over the 24 hours. His minimum figure is in fairly close agreement with that arrived at in the experiments of Chittenden and his co-workers (101) who found that a minimum intake of 50 grams of essential protein was necessary for body wellbeing.

Too often the diagnosis of chronic interstitial nephritis leads to a drastic cutting down of the protein content of the diet with, as has already been emphasised, disastrous results upon the general condition. But it has to be remembered that chronic interstitial nephritis is a slow progressive condition; that there are various degrees of severity in the disease; and that it is now possible to diagnose the condition at a much earlier stage by means of the renal efficiency tests. Consequently there should also be degrees in the cutting down of the protein content of the diet. The rate at which protein is reduced in the diet should be parallel with the advance of the condition, only as much protein being allowed as/

TABLE VI.

a) showing average urea excretions over period with definite protein intakes.
J.D.S.C. body weight 8 st.11 lbs.-9 st.4 lbs. Urea range max.3.8%, min.0.4%.

Diet etc.	Night	1 p.m.	5 p.m.	10 p.m.	Urea conc.	24 hours Amt.	Urea output
	%	%	%	%	%	ccs.	grams
1 up	2.2	1.1	0.7	1.1	1.1	1100	12.1
2 up	2.1	1.31	0.8	1.2	1.3	1190	15.47
3 up	2.8	1.55	1.2	1.8	1.9	1230	23.37
4 up	3.15	1.81	1.4	2.1	2.1	1280	26.88

---

b) Highest and lowest concentrations over same period.

Diets	1 up	2 up	3 up	4 up
Highest	2.7	2.85	3.2	3.3
Lowest	0.55	0.6	1.05	1.25

TABLE VII.

a showing average urea excretions over period with definite protein intakes.
Mrs.McV. body weight on admission 9 st. 1¼ lbs. Urea range, max. 4.5%, min. 0.35%.

Diet etc.	Night %	Noon %	4.30 p.m. %	9 p.m. %	Urea conc. %	24 hours Amt. ccs.	Urea output grams	Body weight
1 in bed	2.66	0.96	1.43	1.24	1.29	1375	15.852	9 st. 1 lb.
2 in bed	2.7	1.01	1.56	1.88	1.51	1179	17.803	8 st. 10 lbs.
3 in bed	3.35	1.65	1.79	1.54	1.81	1347	24.381	9 st.
4 up	2.85	1.67	2.22	1.76	1.99	1333	26.527	8 st. 13 lbs.
3 up	3.13	1.7	2.2	1.52	1.96	1262	24.735	8 st. 12 lbs.

---

b Highest and lowest concentrations over same period.

Diets	1 in bed	2 in bed	3 in bed	4 up	3 up
Highest	3.45	3.15	3.7	3.8	3.4
Lowest	0.48	0.4	0.7	1.3	1.25

TABLE VIII.

a) showing average urea excretions over period with definite protein intakes.
M.H. body weight on admission 6 st. Urea range, maximum 3.8%, minimum 0.3%.

Diet etc.	Night %	Noon %	4.30 p.m. %	9 p.m. %	Urea conc. %	24 hours Amt. ccs.	Urea output grams	Body weight
1 in bed	2.19	1.06	0.9	1.0	1.1	1115	12.173	6 st. 13½ lbs.
2 in bed	2.19	0.76	0.7	0.9	1.05	1202	12.55	6 st. 13 lbs.
3 in bed	2.95	1.88	1.7	1.23	1.77	1170	20.51	7 st. 3½ lbs.
4 up	2.91	1.89	1.9	1.76	2.05	1120	22.78	7 st. 4½ lbs.
3 up	2.41	1.2	2.3	1.85	1.99	1060	20.584	6 st. 13 lbs.
2 up	1.66	0.94	1.4	0.7	1.185	1222	14.23	6 st. 10 lbs.

---

b) Highest and lowest concentrations over same period.

Diets	1 in bed	2 in bed	3 in bed	4 up	3 up	2 up
Highest	2.45	2.2	3.5	3.2	3.3	2.2
Lowest	0.43	0.43	0.35	1.25	1.0	0.5

Excretion of Urea on Diets of varying Protein Content.

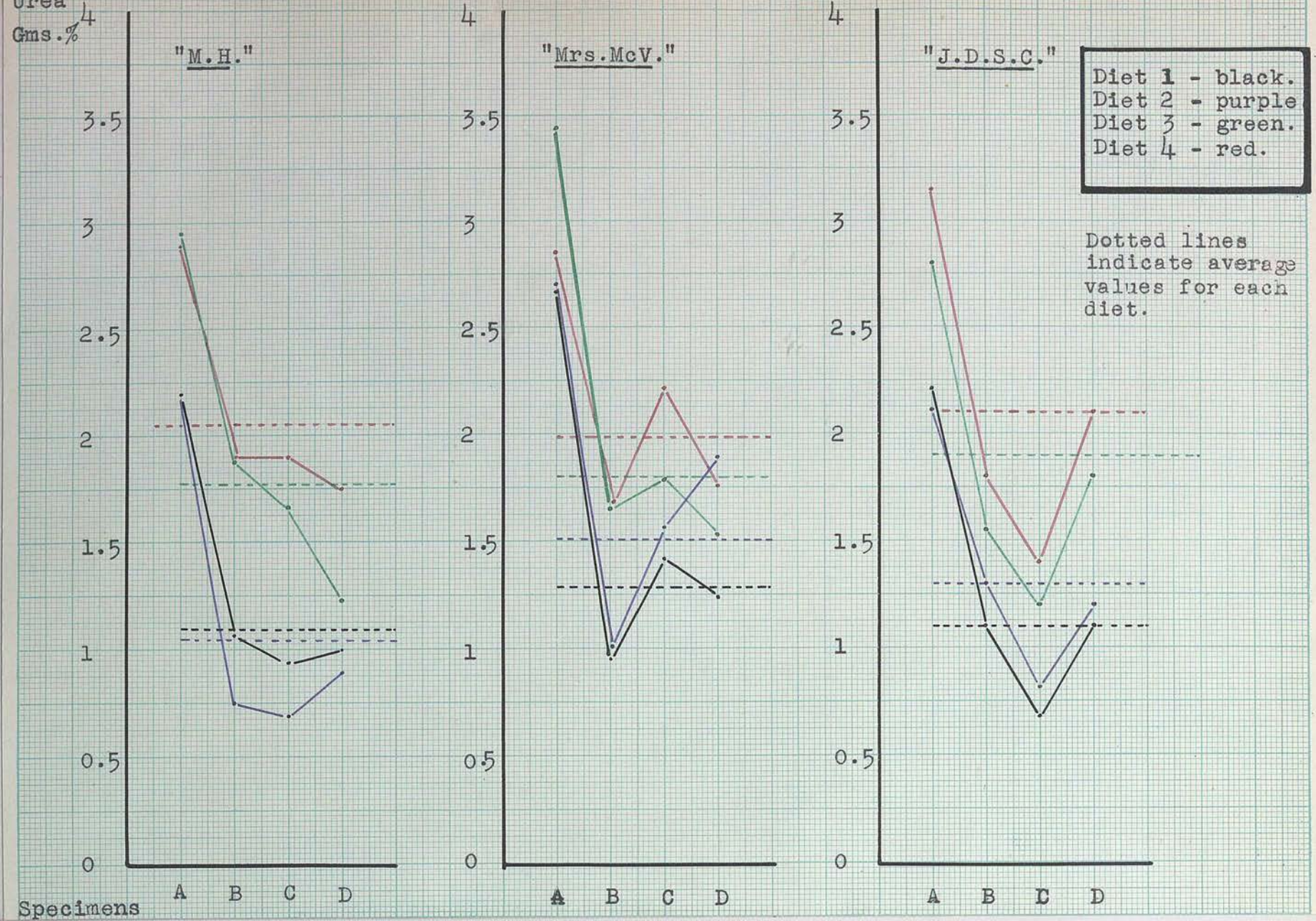


CHART IV

as will produce urea which can be eliminated by the diseased kidney without heaping up of that metabolite in the blood. By means of the urea range the maximum ability of the kidney to excrete urea can be ascertained and so an opinion can be formed as to the degree of the disease. As already suggested the amount of protein allowed in the diet should be such as will yield urea which will never call upon more than two thirds to three fourths of this maximum ability. It was with this in view that the above-mentioned patients were placed on varying protein diets, so that the urea demands of known intakes of protein might be ascertained. The results obtained personally and in two of these patients are given in tabular and graphic form - the figures quoted being averages over the period during which the special diet was given (Tables VI VII & VIII and Chart IV).

In these tables several points of importance have to be observed:

1. The concentrating power of the kidneys varied greatly at different times of the day, this being due to the changes in the body's needs for the elimination of water. In all instances the concentration of urea in the night urine was greater than that in the day urine.

2. In all three cases the urea elimination rose with the/

the increase in protein intake. With Diet I the patients were not in nitrogen equilibrium, and this accounted for the non-proportionate increase in urea output when Diet 2 was substituted.

3. The highest urea concentration observed called for the utilisation of almost all the kidney reserve power in all cases. J.D.S.C. showed a maximum urea range of 3.9% and a concentration of 3.6% was called for while on the diet of highest protein content. In the case of M.H. the urea range showed a maximum ability of 3.8%, and the highest urea concentration during the period of observation was 3.5%. The urea range of Mrs. McV. showed a maximum ability to concentrate of 4.5% while over the observed period the highest demand put upon the kidney was to concentrate to 3.8%.

4. Even on the diet with highest protein content the average daily concentration did not exceed 2% in any case. This bears out the statement that an average daily excretion of 2% is sufficient to meet the needs of the body. With this 24 hours' average, however, the cases showed a highest average concentration by night respectively of 3.1%, 2.9% and 2.85% over the same period. Thus to maintain such an average 24 hours' concentration a greater ability to concentrate must be present.

5./

5. The highest average outputs of urine over the 24 hours were 1190 ccs., 1222 ccs., and 1375 ccs. respectively. The intake of fluid was maintained within normal limits over the experiment but was in no way restricted.

Noting these points it would seem that the protein content of the diet to a great extent regulates the urea content of the urine, and that variation in urea output is roughly parallel to the change in protein intake. Consequently if a fixed protein content of the diet be maintained over a period the total urea elimination should also remain constant. If this be combined with a normal and known fluid intake the average concentration of urea in the urine over the 24 hours should also remain fairly steady.

Application of experimental diets to treatment of chronic interstitial nephritis.

As has already been observed, the aim in treatment of chronic interstitial nephritis should be to give as liberal a protein diet as is consistent with the renal ability to excrete urea, thereby maintaining the general condition at as high a plane as possible and at the same time preventing any retention of urea in the blood. For this purpose it is suggested that the urea range should be used to classify the case as regards/

regards degree of chronic interstitial nephritis. If the case falls into the first group of very early chronic interstitial nephritis the kidney is still capable of concentrating urea to 3% or more. Even with the highest diet used (120 grams of protein) the average daily concentration was 2% and an ability to concentrate above 3% was practically never required. Thus no more than two thirds of the tissue was being called upon to function, and so at this stage the highest protein content diet can safely be given. As, however, this diet contains more protein than the normal individual requires, though it can safely be given, the need for it is seldom present, and so by giving the diet immediately next to it containing 96 grams of protein, abundant protein is being administered while at the same time the margin of safety is increased.

In the second stage (moderate chronic interstitial nephritis) the maximum renal concentration ability is at least 2.5%. Following the procedure of allowing two thirds to three fourths of this ability to be utilised for an average daily concentration it will be seen that the third diet reaches to the limit, this necessitating a daily average concentration of 1.8% while the highest concentration called for may reach 3%. This, however, could be countered by a higher concentration/

concentration at a later period or by a slight increase in the amount of fluid excreted. Thus at this stage, while 96 grams of protein may safely be given per diem, it is advisable, if possible, to remain below this maximum and so ensure that no retention will occur. For this type of case Langdon Brown's (95) maximum of 94 grams is probably applicable.

With the advance of the condition to the third stage of definite chronic interstitial nephritis the intake has to be further reduced. Diet 2 with 73 grams of protein necessitating an average daily concentration of 1.5%, is suitable. The maximum ability at this stage, as shown by urea range, lies between 2% and 2.5% and therefore only two thirds to three fourths of the available renal tissue would be utilised to maintain the necessary average concentration for this diet.

In the second last stage of the condition, advanced or subterminal chronic interstitial nephritis, only the bare minimum of protein can be given. Diet 1 contains 50 grams of protein and this amount necessitates an average daily concentration of up to 1.29%. With this amount of protein, however, the body is not in nitrogen equilibrium. Chittenden showed that 50 grams of essential protein was necessary per diem. Consequently/

Consequently 50 grams of mixed protein will not maintain general condition and so Diet 1 cannot be considered as a suitable one. Diet 2 contains more protein yet entails little increase in urea elimination and so for this stage it is desirable, despite the fact that it may be slightly above the ability of the kidneys to deal with it normally. In most cases a little extra water elimination will lead to the clearance of the urea; or, if need be, its protein content may be slightly reduced. This is in agreement with Langdon Brown's minimum protein intake of 60 grams.

With the advance of the condition to the terminal stage treatment is little more than palliation. The ability of the organ to deal with nitrogen has now fallen to such an extent that it is practically incapable of dealing with even endogenous nitrogen. Nitrogenous accumulation must inevitably continue and death from uraemia must result in a matter of weeks. By the time this stage has been reached, gastro-intestinal symptoms are almost certainly present and these will in the main regulate the type of diet which can be given.

Thus in the treatment of chronic interstitial nephritis it is suggested that the amount of protein given/

given should be regulated by the urea range findings, the intake decreasing with advance of the condition as shown by the urea range. In the recovery stage of acute parenchymatous nephritis the same procedure should be adopted, the diet given being increased as the ability of the kidney to deal with the azotaemic products is shown to improve. Thus the maximum ability in this condition rapidly increases to 2.5% with the disappearance of the blood from the urine, and with this ability Diet 2 can safely be given. After this the functional ability returns more slowly but with a return to 3%, Diet 3 can be given, and then the highest protein diet (Diet 4) should follow when the maximum ability rises to 3.5% and the patient is allowed up. In this way accumulation of nitrogenous constituents in the blood is easily guarded against, while the fullest amount of protein is given to aid the recovery of the physical condition.

The above dietetic considerations in the treatment of chronic interstitial and acute parenchymatous nephritis can be conveniently summarised in tabular form.

form.

Degree of impairment	Maximum urea conc. ability	Diet recommended	Average 24 hours urea conc. required
Stage 1 very early	3% - 3.5%	Diet 4 Diet 3	2% 1.8%
Stage 2 moderate	2.5% - 3%	Diet 3	1.8%
Stage 3 definite	2% - 2.5%	Diet 2	1.5%
Stage 4 advanced or subterminal	1.5% - 2%	Diet 1	1.5%
Stage 5 terminal	less than 1.5%	As for stage 4, or symptomatic	

SUMMARY.

1. The function of the kidneys is the maintenance of a constancy in blood composition. The subfunctions of the kidneys directed towards this maintenance are discussed.
2. The literature of blood chemistry in its application to renal function is reviewed.
3. The renal efficiency tests are classified and discussed.
4. The necessities of the ideal renal efficiency test are stated and applied to the above tests.
5. Urea appears the most suitable substance for use in the ideal efficiency test. This suitability is investigated as regards a) non-injuriousness to body tissues; b) ease of estimation; c) amount required to call forth full action of "resting and reserve forces" of kidneys.
6. Following review of the urea tests at present in use, the urea concentration range of Calvert is regarded as that most nearly approaching the ideal.
7. The urea range of normal individuals is ascertained following application to 108 such cases. This investigation showed a) normal urea concentration range - maximum, 3.5%-4.0%, minimum, 0.3%-0.4% at all/

all ages; b) necessity for restriction of fluid intake; c) suitability of 15 grams of urea as amount calling for full kidney action.

8. Application and interpretation of the test is made in pathological conditions (504 cases): a) non-renal high blood pressure; b) chronic interstitial nephritis and congenital cystic kidney; c) "mixed" nephritis; d) chronic parenchymatous nephritis and nephrosis; e) acute parenchymatous nephritis; f) non nephritic haematuria; g) "prostatism"; h) cardiac conditions; i) non nephritic urinary conditions; j) orthostatic albuminuria.
9. The value of the test in diagnosis and prognosis of above conditions is discussed.
10. Treatment of these conditions is indicated, this being based upon the degree of renal efficiency as demonstrated by the urea concentration range.

The investigations reported in this study were carried out in the wards of the Royal Infirmary, Edinburgh, under the charge of Dr. Edwin Matthew; and at the Highbury Group of Hospitals (Ministry of Pensions), Moseley, Birmingham.

APPENDIX I.

DIETS SUGGESTED IN TREATMENT OF ACUTE PARENCHYMATOUS NEPHRITIS AND CHRONIC INTERSTITIAL NEPHRITIS.

APPENDIX I.

Milk, glucose and fruit juice diet for the initial stage of acute parenchymatous nephritis.

(The glucose fruit juice mixture is a 30% solution of glucose in water with the juice of 1 or 2 oranges or lemons added to each pint for flavouring purposes).

8 a.m.	6 ozs. milk
10 a.m.	5 ozs. glucose fruit juice mixture
12 noon	6 ozs. milk
2 p.m.	5 ozs. glucose fruit juice mixture
4 p.m.	6 ozs. milk
6 p.m.	5 ozs. glucose fruit juice mixture
8 p.m.	6 ozs. milk
During night	5 ozs. glucose fruit juice mixture.

With improvement in condition the milk can be wholly or partly substituted by milk and cream mixture(Sippy (186)) while bread and butter, Benger, arrowroot or other light cereals may be added.

When the urea concentration range shows a maximum ability of 2.5% Diet 2 (as given for chronic interstitial nephritis) is given. With rise in maximum to 3% Diet 3 is used, while a maximum of 3.5% or over permits of the use of Diet 4.

DIETS SUGGESTED FOR USE IN TREATMENT OF CHRONIC INTERSTITIAL NEPHRITIS.

Degree of impairment	Maximum urea conc. ability	Diet recommended	Average 24 hours urea conc. required
Stage 1 very early	3% - 3.5%	Diet 4 Diet 3	2% 1.8%
Stage 2 moderate	2.5% - 3%	Diet 3	1.8%
Stage 3 definite	2% - 2.5%	Diet 2	1.5%
Stage 4 advanced or subterminal	1.5% - 2%	Diet 1.	1.5%
Stage 5 terminal	less than 1.5%	As for Stage 4, or symptomatic	———

DIET I.

Ch.260 Prot.50 Fat 84 Calories 2006

BREAKFAST	4 tablespoons porridge 1½ ozs. bread 1 tablespoon marmalade or jam Butter, milk and sugar from ration Tea
FORENOON	1 orange
DINNER	1¾ ozs. meat 6½ ozs. vegetable 3½ ozs. potato ¼ oz. cornflour, sago, arrowroot, or tapioca with milk from ration. 3½ ozs. stewed apple with sugar from ration
TEA	3½ ozs. tomato and lettuce salad now or at supper 1½ ozs. bread Milk and butter from ration. Tea 1 tablespoon jam now or at supper
SUPPER	1½ ozs. bread Butter from ration Glass of milk 1 tablespoon jam now or at tea

RATIONS FOR DAY

10 ozs. vegetable
3½ ozs. potato
3½ ozs. orange
3½ ozs. apple
4 tablespoons porridge
5 ozs. bread
¼ oz. cereal(cornflour, sago, arrowroot or tapioca)
2 tablespoons jam or marmalade
1½ ozs. sugar
½ pint milk
1¾ ozs. meat
2¼ ozs. butter or margarine.

DIET 2.

Ch.288 Prot.73 Fat 73 Calories 2101
(Lowest urea range maximum 1.5%).

BREAKFAST
4 tablespoons porridge
1¼ ozs. bread
1 tablespoon marmalade or jam
Milk, butter and sugar from ration
Tea

LUNCH
Milk from ration

DINNER
5% vegetable 7 ozs. with butter from ration
3½ ozs. potato
3½ ozs. apple - stewed with sugar from ration
¼ oz. arrowroot, sago, cornflour or tapioca with milk and sugar from ration
2 ozs. meat

TEA
3½ ozs. lettuce and tomato salad
1½ ozs. bread
1 tablespoon jam
1 egg
Butter, sugar, milk from ration
Tea

SUPPER
3½ ozs. orange
2 ozs. bread
Milk, sugar, butter from ration.

RATIONS FOR DAY

2 ozs. butter or margarine
1 pint 7½ ozs. milk
5% vegetable 10 ozs.
3½ ozs. potato
1 tablespoon jam
1 tablespoon marmalade
3½ ozs. apple
3½ ozs. orange
4 tablespoons porridge
4¾ ozs. bread
¼ oz. cereal
1¼ oz. sugar.

DIET 3.

Ch.266 Prot.96 Fat 95 Calories 2303
(Lowest urea range maximum 2.5%).

BREAKFAST
5 tablespoons porridge
1 egg
1½ ozs. bread
1 tablespoon marmalade
Butter and milk from ration
Tea

FORENOON
3½ ozs. orange - peeled weight, or 2¼ ozs. apple

DINNER
2 ozs. meat
7 ozs. vegetable
3½ ozs. potato
¼ oz. cornflour, arrowroot, sago or tapioca as pudding with milk and sugar from ration
3½ ozs. apple - stewed with sugar from ration or raw

TEA
3½ ozs. tomato or lettuce now or at supper
1 egg
2 ozs. bread
½ oz. cheese
Butter and milk from ration
Tea

SUPPER
3 ozs. fish
1½ ozs. bread
Butter from ration
Tea, or milk from ration to drink.

RATIONS FOR DAY

14 ozs. vegetable
3½ ozs. potato
3½ ozs. orange
3½ ozs. apple
4 tablespoons porridge
5 ozs. bread
1¾ ozs. sugar
1 tablespoon jam or marmalade
¼ oz. cereal - cornflour, arrowroot, sago or tapioca
1 pint milk
2 eggs
2 ozs. meat
½ oz. cheese
3 ozs. fish
1½ ozs. butter.

DIET 4.

Ch.216 Prot.120 Fat 128 Calories 2496
(Lowest urea range maximum 3%).

BREAKFAST
5 tablespoons porridge
1 egg
1½ ozs. bacon
1¼ ozs. bread
Butter and milk from ration
Tea

DINNER
2½ ozs. meat
7 ozs. vegetable
3½ ozs. potato
¼ oz. arrowroot, sago, cornflour or tapioca with 1 egg and milk and sugar from ration
3½ ozs. fruit stewed or fresh

TEA
3½ ozs. lettuce and tomato salad
1½ ozs. bread
1 egg
1 oz. cheese
Butter, sugar and milk from ration
Tea

SUPPER
4 ozs. fish
1½ ozs. bread
Milk, sugar and butter from ration
Tea

RATIONS FOR DAY

1¼ ozs. butter or margarine
1 pint milk
10 ozs. 5% vegetable
3½ ozs. potato
3½ ozs. orange or 2½ ozs. apple
4½ ozs. bread
1½ ozs. sugar
2½ ozs. meat
1½ ozs. bacon
1 oz. cheese
4 ozs. fish.

APPENDIX II.

FURTHER ILLUSTRATIVE CASES.

N O R M A L.

Name	Sex	Age	Urea conc. range percentage Maximum	Minimum	Remarks.
J.S.	F.	25	4.6	0.45	-
Mrs. W.	F.	52	3.5	0.3	Hyperthyroidism
M.D.	F.	22	3.6	0.3	-
B.D.	F.	34	4.0	0.3	Endocrine dysfunction
Mrs.H.	F.	40	4.0	0.25	Gastric ulcer
Mrs.F.	F.	53	3.7	0.2	Cerebral thrombosis with hemiplegia
Mrs.L.	F.	58	3.8	0.35	-
M.H.	F.	13	3.5	0.35	Convalescent after pneumonia
Mrs.R.	F.	54	3.8	0.3	Paroxysmal tachycardia
M.D.	F.	19	3.5	0.3	Convalescent after pneumonia
G.S.	M.	49	3.5	0.4	Tobacco amblyopia
Mrs.G.	F.	52	3.5	0.3	Epilepsy
Mrs.G.	F.	51	3.6	0.35	Rheumatoid arthritis
Mrs.S.	F.	41	4.6	0.35	Hyperthyroidism
- B.	M.	--	3.5	0.45	-
Mrs.McV.	F.	27	a) 4.2	0.4	15 grams urea
			b) 4.3	0.35	20 grams urea
Pens.T.	M.	34	3.8	0.4	
Pens.M.	M.	36.	4.4	0.4	
Pens.T.	M.	31	3.5	0.35	
Pens.C.	M.	38	3.6	0.3	
Pens.F.	M.	40	4.0	0.4	All orthopaedic cases
Pens.McD.	M.	41	3.6	0.4	
Pens.M.	M.	29	3.6	0.3	
Pens.S.	M.	34	3.7	0.5	
Pens.B.	M.	32	3.8	0.35	

N O R M A L. contd.

Name	Sex	Age	Urea conc. range percentage Maximum	Minimum	Remarks.
Mrs.C.	F.	48	3.5	0.3	Phenolsulphonephthalein 15+10=25% Diastase test 10 units
Mrs.S.	F.	54	4.5	0.4	
Mrs.Y.	F.	22	3.5	0.2	Recent eclampsia
Mrs.F.	F.	49	4.0	0.3	
J.F.	M.	34	3.6	0.2	Pulmonary tuberculosis
J.S.	M.	12	3.7	0.3	Abdominal tuberculosis
B.C.	F.	25	3.5	0.3	Rheumatoid arthritis
J.H.	F.	24	4.0	0.15	Gonoccal arthritis
J.H.	F.	13	4.2	0.3	Angio neurotic oedema
J.M.	F.	22	4.2	0.4	Constipation
J.M.	M.	80	3.5	0.4	Note age
H.L.	M.	37	3.5	0.4	Causalgia
J.T.	M.	30	3.6	0.4	Hyperchlorhydria
M.M.	F.	33	4.0	0.3	Rheumatoid arthritis
M.B.	F.	4	4.0	0.2	10 grams urea - note age
G.M.	M.	11	3.5	0.3	Rheumatoid arthritis
Mrs.K.	F.	50	3.5	0.4	Diabetes mellitus, no diuresis
A.B.	F.	25	4.0	0.2	Rheumatoid arthritis
J.K.	M.	43	3.9	0.4	Neurasthenia
Mrs.S.	F.	52	4.0	0.4	Adhesions
Mrs.S.	F.	55	4.0	0.3	Neuralgia
Mrs.S.	F.	31	3.8	0.3	Rheumatoid arthritis

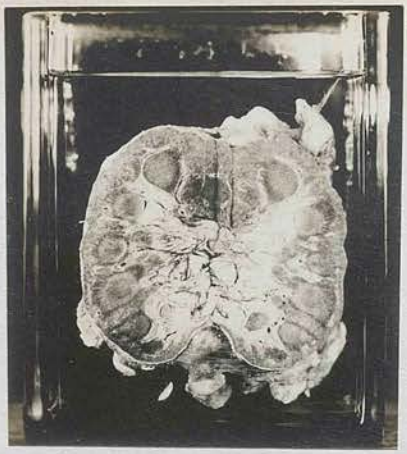
HIGH BLOOD PRESSURE OF NON NEPHRITIC ORIGIN.

Name	Sex	Age	Urea conc. range Maximum %	Urea conc. range Minimum %	Blood pressure	Remarks
A.I.	M.	58	4.0	0.35	290/160	Blood urea 24 mgms. per cent.
Mrs.A.	F.	67	3.8	0.35	260/160	Normal blood urea. Early cardiac failure
J.N.	M.	61	3.5	0.4	220/140	Seven years previously blood pressure 195/120
Mrs.A.	F.	60	3.5	0.4	235/145	- -
J.C.C.	M.	54	3.8	0.45	170/100	Anginal attacks
Mrs.B.	F.	56	4.0	0.4	210/140	---
J.H.	F.	47	3.6	0.4	240/140	Menopause
Mrs.D.	F.	58	4.1	0.3	195/115	Cardiac failure. No oedema
J.R.	M.	48	4.0	0.5	200/110	Angiospasm
Mrs.G.	F.	41	4.0	0.4	185/100	Menopause
J.McE.	M.	64	3.7	0.5	200/100	- - -
K.M.	M.	49	3.5	0.6	290/190	Cramps in legs. Epistaxis
E.L.	F.	67	3.6	0.4	240/120	- - -
M.G.	F.	58	3.8	0.4	220/130	- - -
Mrs.T.	F.	60	4.3	0.3	240/150	- - -

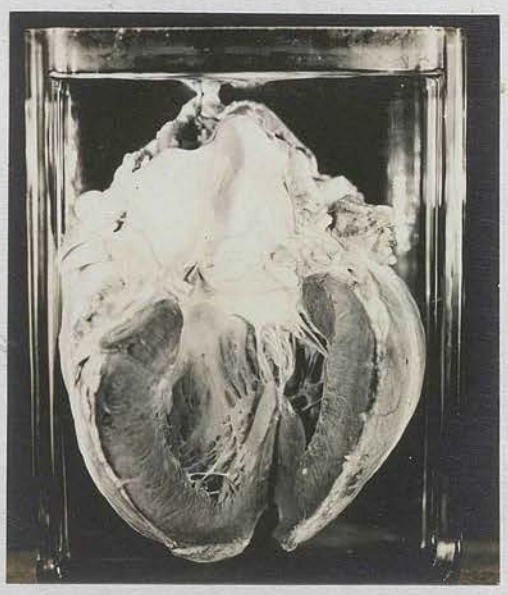
CHRONIC INTERSTITIAL NEPHRITIS.

Name	Sex	Age	Urea conc. range Maximum %	Urea conc. range Minimum %	Blood pressure	Blood urea mgms.%	Remarks
B.McK.	F.	64	1.4	0.5	198/140	160	- -
Mrs.E.	F.	42	1.9	0.6	210/160	60	First admission
			Too ill for repetition		230/160	120	2nd admission. Death from uraemia.P.M. (fig.42)
A.L.	F.	25	1.1	0.8	220/165	200	Death,uraemia. P.M. (Fig.43)
Mrs.H.	F.	60	1.6	1.0	---	---	Uraemic asthma
M.C.	M.	59	2.7	0.45	190/110	40	Early cardiac failure
J.C.	M.	52	2.3	0.7	220/150	50	- -
Mrs.M.	F.	60	2.35	0.6	250/170	60	Cerebral haemorrhage
J.G.	M.	65	1.85	1.0	210/150	80	Prostate also enlarged
Mrs.G.	F.	52	1.35	0.9	300/190	95	Hemiplegia
Mrs.N.	F.	53	1.45	0.8	284/190	148	Death from uraemia.P.M.
Mrs.W.	F.	56	1.1	0.9	240/160	105	Death from uraemia.P.M.
Mrs.S.	F.	28	1.1	0.95	235/160	200	Death from uraemia. No P.M.
Mrs.M.	F.	54	1.8	0.7	200/145	65	- -
Mrs.F.	F.	52	1.3	0.5	195/135	110	Death from uraemia.P.M.
Mrs.F.	F.	52	a) 3.05	0.6	190/110	34	On first admission
			b) 2.85	0.6	200/110	38	Four months later
Mrs.B.	F.	73	1.45	0.55	- - -	84	- -
J.W.	M.	65	1.6	0.7	240/170	110	Death four months later from uraemia
Mrs.McG.	F.	41	a) 2.15	0.3	215/160	70	- -
			b) 1.6	0.7			
Mrs.L.	F.	56	a) 2.4	0.3	- -	-	15 grams urea
			b) 2.4	0.3	- -	-	20 grams urea

a)



b)



c)

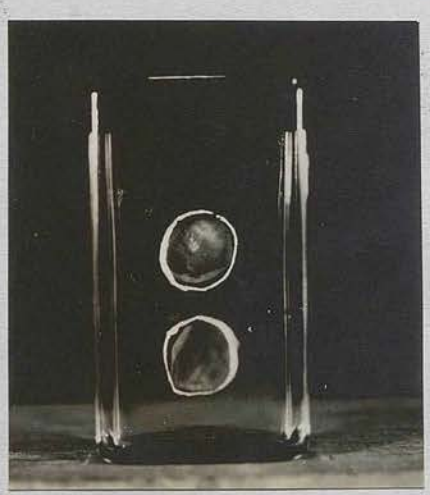


Fig. 49. Mrs. B. (aet.64). Chronic interstitial nephritis. Death from uraemia.
a) left kidney showing interstitial changes.
b) heart showing left ventricular hypertrophy.
c) retinae showing albuminuric retinitis and haemorrhages.
Urea Concentration Range: Maximum, 1.1%; minimum, 0.8%.
Blood urea, 212 mgms. per cent.

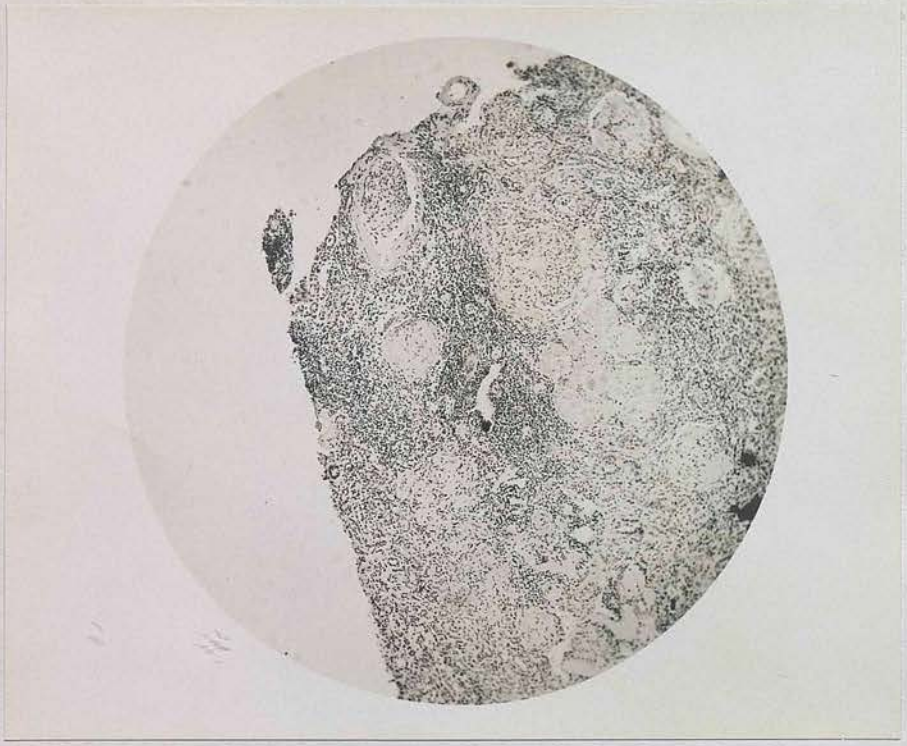


Fig. 50. Mrs. B. (aet.64). Chronic interstitial nephritis. Death from uraemia.
d) L.P. kidney (x 56) showing advanced chronic interstitial nephritis.
Urea Concentration Range: Maximum, 1.1%; minimum, 0.8%
Blood urea 212 mgms. per cent.

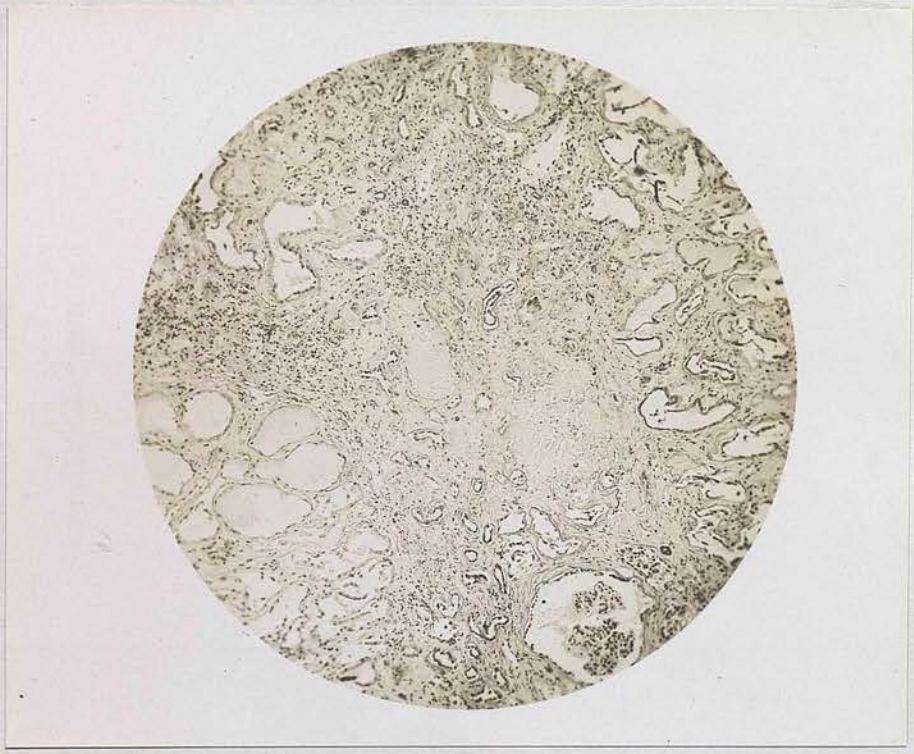


Fig.51. J.C. (aet.19). Section of kidney shows chronic interstitial nephritis (x 56). Blood urea 200 mgms.%. Urea Concentration Range: maximum, 1.2%; minimum, 0.9%. Blood pressure 198/140. Death from uraemia.

CHRONIC INTERSTITIAL NEPHRITIS (contd.).

Name	Sex	Age	Urea conc. range Maximum %	Urea conc. range Minimum %	Blood pressure	Blood urea mgms.%	Remarks
Mrs.McV.	F.	52	a) 2.1	0.6	195/120	42	- -
			b) 2.0	0.6	- -	-	- -
			c) 2.0	0.6	200/130	-	Death from cellulitis. No P.M.
J.L.	M.	60	2.7	0.7	220/145	48	- -
D.W.	M.	--	a) 1.2	4.7	210/150	134	Death from uraemia. P.M.
			b) 1.1	0.8	- --	-	- -
Mrs.B.	F.	65	a) 1.0	0.8	220/150	200	Death from uraemia. P.M. (figs.48)
			b) 1.1	0.8	- -	-	- -
J.M.	M.	54	1.3	0.9	195/130	148	Death from uraemia. No P.M
Pens.H.	M.	47	1.3	1.0	200/145	105	Death from uraemia. P.M.
Pens.W.	M.	38	2.3	0.5	158/100	30	- -
A.A.	M.	60	2.5	0.5	164/110	35	Diastase test 10+ Phenolsulphonephthalein - 15+45=60
J.C.	M.	19	1.2	0.9	198/140	200	Death from uraemia. P.M. (fig. 57)

"PROSTATISM"

Name	Age	Urea conc. range percentage Maximum	Minimum	Remarks
W.D.	53	1.1	0.65	Blood urea 82 mgms. per cent.
J.R.	58	1.75	0.75	Blood urea 68 mgms. per cent.
J.W.	78	1.8	1.3	Chronic bronchitis
W.R.	--	2.6	1.4	---
W.R.	64	1.1	0.4	Cancer and infection of prostate

CARDIAC CONDITIONS.

Name	Sex	Age	Urea conc. range percentage Maximum	Minimum	Remarks
Mrs.McN.	F.	48	3.8	0.3	Mitral stenosis. No oedema
J.J.	M.	66	a) 1.8	1.1	Aortic aneurism - oedema
			b) 2.7	0.7	Oedema disappearing
Mrs.T.	F.	-	3.0	0.5	Mitral stenosis with oedema
Mrs. A.	F.	50	3.6	0.35	Aortic incompetence and aneurism- No oedema
Mrs.G.	F.	55	a) 2.9	0.4	Pulmonary tumour - early oedema
			b) 1.9	0.4	Pulmonary tumour - much oedema
- V.	M.	50	2.2	0.3	Lung tumour with cardiac failure
Mrs.N.	F.	60	5.0	0.25	Senile myocarditis.Auricular fibrillation
W.D.	M.	--	3.5	0.4	Aortic incompetence - no cardiac failure
Pens.H.	M.	30	3.2	0.4	Mitral stenosis - auricular fibrillation
Pens.R.	M.	32	1.2	0.35	Bronchitis and emphysema. Cardiac failure P.M. no renal lesion
Mrs.S.	F.	56	a) 3.2	0.4	Auricular fibrillation and myocarditis Phenolsulphonephthalein 45+15=60
			b) 3.6	0.4	Prior to discharge
A.L.	M.	30	1.8	0.3	Mitral stenosis with oedema
A.McI.	M.	50	1.55	0.3	Myocarditis
H.F.	F.	65	3.8	0.3	Cancer of breast and lung
Mrs.C.	F.	45	4.0	0.3	--
Mrs.C.	F.	39	2.7	0.5	Auricular fibrillation - bronchitis
J.H.	M.	53	3.8	0.3	Aortic incompetence
J.P.	F.	14	4.4	0.4	Mitral stenosis - no oedema
Mrs.H.	F.	58	4.0	0.3	Aortic aneurism

ACUTE PARENCHYMATOUS NEPHRITIS.

Name	Sex	Age	Urea conc. range percentage Maximum	Minimum	Remarks
W.McI.	M.	28	a) 2.05	0.65	On admission - a clearing case
			b) 2.8	0.65	Seven days after admission
			c) 3.5	0.4	Twenty-one days after admission
J.S.	M.	59	a) 1.35	0.4	One week after admission
			b) 3.7	0.4	On discharge
J.C.	F.	13	a) 2.4	0.6	Six weeks after admission
			b) 3.3	0.4	Nine weeks after admission
			c) 3.5	0.25	Eleven weeks after admission
Mrs.M.	F.	22	a) 1.7	0.3	Three weeks after admission
			b) 3.2	0.3	Five and a half weeks after admission
Mrs.D.	F.	45	a) 2.7	0.4	Four weeks after admission
			b) 3.8	0.35	Twelve weeks after admission
E.McG.	M.	27	a) 2.3	0.3	Four weeks after admission
			b) 2.65	0.3	Six weeks after admission
			c) 3.6	0.3	Ten weeks after admission
J.F.	M.	35	a) 2.4	0.9	Four weeks after admission
			b) 3.4	0.4	Nine weeks after admission
J.McG.	M.	8	a) 1.8	0.3	After disappearance of albumin
			b) 2.8	0.3	Four weeks later
M.McK.	F.	15	2.5	0.8	No albumin in urine
W.P.H.	M.	17	a) 1.85	-	Trace of albumin in urine
			b) 2.9	0.6	Four weeks later
Mrs.M.	F.	29	a) 3.0	0.5	Albumin free for two weeks
			b) 3.2	0.5	One week later
D.N.	M.	46	1.1	0.6	On admission

"MIXED NEPHRITIS"

Name	Sex	Age	Urea conc. range percentage Maximum	Minimum	Remarks
A.M.	M.	52	a) 2.5	0.45	
			b) 1.6	0.8	Six months later
J.W.	M.	51	3.15	1.5	Heavy albuminuria
N.McK.	F.	21	1.2	1.0	Death P.M.
L.S.	F.	25	1.0	0.4	Death P.M.
A.K.	M.	38	2.1	0.55	Albumin 0.4 grains per ounce. Oedema.

NON NEPHRITIC URINARY CONDITIONS.

Name	Sex	Age	Urea conc. range percentage Maximum	Minimum	Remarks
J.I.	F.	20	4.2	0.3	Cystitis
A.H.	M.	21	5.0	0.25	Oxaluria
A.P.	F.	22	3.5	0.3	Haematuria
Pens.P.	M.	29	3.9	0.4	Oxaluria
Mrs.P.	F.	32	3.7	0.2	Renal colic
J.W.W.	M.	26	4.0	0.2	Ulceration of bladder
J.G.	M.	18	3.5	0.3	Orthostatic albuminuria
A.R.B.	M.	39	3.5	0.2	Renal glycosuria
J.C.	M.	15	3.5	0.3	Orthostatic albuminuria

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