RENAL EFFICIENCY TESTING: THE UREA CONCENTRATION RANGE IN DIAGNOSIS AND PROGNOSIS OF KIDNEY INEFFICIENCY.*

By J. D. S. CAMERON, M.D., F.R.C.P.E.

Functions of the Kidney.—Despite centuries of research, dating probably even from before Malpighi[13] (1628-61), the exact mode of functioning of the kidney remains unelucidated. No theory of kidney function is yet acceptable to all. But theory is of comparatively little importance clinically. Sufficient that the function itself is fairly clear, for knowing what it does, we can endeavour to ascertain how it may go wrong. Before we can consider how its functional ability may be tested, it will be easier to delay for a minute to consider the functions we set out to test. "Only by knowing the normal can we appreciate departure from it."

The kidney serves to maintain a constancy in the composition of the blood, excreting from it any substance which tends to produce departure from this constancy. An apparently simple function until it is analysed, then its complexity is appreciated, for this broad function is served in several ways.

1. It maintains blood volume—a function with which is bound up the maintenance of saline concentration and osmotic tension of the blood. In man, the tissue fluids must contain 0·6 per cent. NaCl, while at the same time their osmotic tension is chiefly maintained by approximately 6 grams of protein, albumin and globulin being in ratio of 2 to 1. It is easy to control blood volume by water elimination or retention, but it becomes much more difficult when constant saline and constant protein concentrations have also to be considered.

2. Blood reaction has to be maintained at *p*H 7·4 by the excretion of either acid or basic ions from the blood. With the aid of the buffer mechanisms of the blood, this function is comparatively easy of accomplishment.

3. The elimination of metabolic waste products is the function upon which attention is usually focussed. The most important of these products are nitrogenous—urea, uric acid, creatinine, and ammonia. Produced within the body from both endogenous and exogenous metabolism, they are usually rapidly excreted from the blood. But as well as simple excretion, let me at this stage draw attention to a very important point—they are highly

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concentrated in their passage from blood to urine, urea 70 to 100 times; uric acid 25 times; and creatinine about 75 times. This concentration power applies to all renal excretions, but from my point of view is most important here. I cannot overemphasise the fact that this concentration power is probably the earliest function to be disturbed when inefficiency commences.

4. Normal blood constituents are not eliminated until present in amount in excess of their threshold value. With such rise, their excretion continues until a level below this threshold is attained. Thus it is assured that even normal and useful constituents are not permitted to produce damage by circulation in increased amounts. The excretion of sugar in hyperglycæmia serves as the best example of this function.

5. Any abnormal entrants to the blood are quickly excreted by the normal kidney. Examples of such substances are the ketone products of defective fat metabolism, bile, bacteria, and toxins. Dye substances have also to be considered here. Introduction either in medicine or in test leads to their clearance independent of their concentration in the blood.

6. In addition to the above excretory functions, the kidney is believed to manufacture certain substances itself—ammonia, hippuric acid, and probably also phosphate.

7. It has been suggested that an internal secretion is furnished by the kidney and is responsible for controlling its function. As yet no definite evidence of such an autacoid has been brought forward, nor does kidney histology show a likely site of production. Kidney function is probably outwith both direct autacoidal and direct nervous control. It is entirely dependent upon the composition and concentration of the blood which passes through it.

Application of these Functions to Renal Efficiency Testing.—Remembering these functions, two facts will become obvious: (1) mere routine examination of the urine is totally insufficient in arriving at a conclusion as to the functional ability of the kidneys; (2) no single test will give full information as to ability.

Regarding the first point, in acute and chronic parenchymatous nephritis, routine examination may serve to establish the diagnosis but will never indicate a true prognosis. In chronic interstitial nephritis it is of even less help, for not until a very advanced stage will departure from normal be found, either in quantity or content. This comparative uselessness of routine examination makes it necessary that other means of testing kidney efficiency be introduced.

The truth of the second fact is apparent and is responsible for the multiplicity of renal efficiency tests. In the region of one hundred such tests have been suggested, but fortunately most of them have been quickly discarded. Considering the space at my disposal a classification of these tests would be wasteful. They all set out to test the efficiency of one or other function and can be conveniently classified accordingly. Let me merely consider those still in common use. But before doing so, allow me to set before you the standards which an ideal efficiency test should reach.

Essentials of the Ideal Efficiency Test.—The test must be (1) easy for the doctor to apply, (2) easy for the patient to carry out; (3) capable of estimation and interpretation without reference to a laboratory or a specialist; (4) the test substance must be non-deleterious to the patient, however ill; (5) the substance must be capable of calling forth the full functional ability of the kidney, for an ideal test must be able to demonstrate the least departure from normal; (6) the substance must be one which the kidney is regularly called upon to deal with; (7) it must be a substance which is not influenced by any other organ in the body.

The necessity of these is almost self-evident. Yet, too often efficiency testing is regarded as a necessarily difficult thing. Should I dispel this idea? If a test is to be a success it should be simple and capable of universal application, and should be one which even the busiest and most modest of practitioners will be ready to apply. In the light of these postulates let me deal with a few of the commonly used tests.

Examination of Tests in Common Use—*Blood Chemistry.*—As the kidney maintains blood chemistry constant, an analysis of blood content might seem sufficient test. Such examination, it may be interesting to note, was practised by Bright himself. In his original papers[4] he noted a high blood-urea content in a uræmic patient, while with Rees[16] he reported "the existence of urea in the blood and effusions obtained from the patients" and in the milk of one. It is admitted that nitrogenous content increases in renal inefficiency, but unfortunately the kidney is well involved in damage before this increase occurs. Verney[18] has shown that of the very large number of renal glomeruli only a few are in action at one time, and so it is possible for the kidney to be markedly impaired before sufficient reduction in the number of these has occurred to give retention in the blood. Beaumont and Dodds[3] note that "some observers state that three-quarters of the kidney must be destroyed before nitrogen

retention appears." Thus blood analysis will afford evidence of advanced damage, but not in those early cases where signs of impairment are slight; and it is in these that help is most required, for kidney damage must be diagnosed while there is yet sufficient active kidney tissue to meet the needs of the body.

Chloride excretion tests are not acceptable, as the kidney is not the only organ dealing with chloride. In most cases the kidney fails to excrete chloride because it never reaches the kidney to be excreted. It is also practically impossible to administer sufficient chloride to call forth the full reserve powers of the kidney without deleterious results to the patient.

Similar objections are raised to the *diastase test* (Wohlgemuth[19]). The excretion of diastase is dependent entirely upon its amount in the blood and this is controlled by hepatic and pancreatic activity. Also, no means has yet been provided of artificially increasing blood-diastase content so 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,[17] Auld,[2] and Comrie,[7] among others, regard the phenolsulphonephthalein (P.S.P.) test as superior to all others, "due to its ease of application, its rapidity of action, and its reliability." But its estimation calls for a method not utilisable by the general physician; it is not a substance normally dealt with by the kidney; and it fails to bring out the full action of the kidney.

The non-protein nitrogenous bodies suggest themselves as substances utilisable in function testing. Uric acid, creatinine, and urea are all in use. The *uric acid test* of Gibson,[8] however, is objectionable as it entails complicated methods of analysis in blood and urine. The same objection has to be raised to the *creatinine tests* of Major[14] and Holten and Rehberg.[10] Not only is the estimation a laboratory procedure but also one which is not regarded as strictly accurate. In my experience[6] little information of renal efficiency has been gained from blood and urine analysis following the administration of 1 gram of creatinine.

Urea Tests.—The importance of urea as a substance for renal efficiency testing is widely recognised and has for long been so. The commonly employed tests which utilise it are:—Ambard's constant[1]; the urea clearance test of Möller, M'Intosh, and van Slyke[15]; the urea concentration factor of Grehant; M'Kaskay's provocative urea test[11]; MacLean and de Wesselow's urea concentration test[12]; and Calvert's urea concentration range.[5] The first three can be immediately dismissed from the

ideal—they require a laboratory estimation of blood urea and, almost as damaging, a knowledge of mathematics. M'Kaskay's test is not employed in this country, being on similar lines to MacLean and de Wesselow's. The last two will require further consideration.

Is urea a non-deleterious substance? It is now generally conceded that it is not the cause of uræmia. Hewlett, Gilbert, and Wickett[9] obtained symptoms of asthenic uræmia following administration of massive doses. In my experience no such symptoms were encountered. Following administration of up to 60 grams in a single dose, the only symptoms felt were those of thirst, polyuria, and frequency. In pathological cases, administration of 25 grams has not been attended by increase in symptoms. It would thus appear that urea is definitely non-deleterious.

Is urinary urea easily estimated? If the sodium hypobromite method be employed, yes; if the urease method, no. The former may be slightly less accurate (it gives a reading of about 94 per cent.), but its ease of application far outweighs this slight inaccuracy. Five specimens can be estimated with ease in ten minutes. Does the complicated urease method obtain greater accuracy in average hands? It may be suggested that the solution of hypobromite used is liable to deterioration, but this is easily overcome. A convenient method is appended.*

Can urea call forth the full reserve power of the kidney? If given in sufficient doses, yes. It is practically a "no threshold" substance and is rapidly excreted by the normal kidney. As already pointed out, also, it is highly concentrated by the kidney, up to or over one hundred times. I found a suitable dose to be that given by MacLean and de Wesselow—15 grams. Experiments were carried out to determine the smallest effective dose. These are detailed in Table I. It will be seen that 15 grams called out practically as full a concentration as any bigger dose and so would appear to be ample. In cases of doubt, 20 grams can conveniently be employed. For young individuals 10 grams was similarly found to be ample, although no objection can be taken to the use of 15 grams there too.

In the light of these results let us consider the remaining two urea tests as possible ideal tests. Both are easy for doctor

* *A.* Sodium bromide 62·5 grams. Bromine 20 c.c. Distilled water 500 c.c. *B.* Sodium hydroxide 22·5 per cent. (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 c.c. of this solution.

and patient to carry out; they are capable of easy estimation and interpretation; urea is non-deleterious; it is normally dealt with by the kidney and is not influenced by any other organ. It is also capable of calling forth the full activity of the kidney when given in an adequate dose.

TABLE I.

Maximum Urinary Concentrations with Varying Urea Intakes.

	5 grm.	10 grm.	15 grm.	20 grm.	25 grm.	30 grm.	50 grm.	60 grm.	Remarks.
	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	
J. D. S. C. .	1·6	2	3·8	3·9	3·8	3·8	3·7	3·6	Normal kidneys.
Mrs M'V. .	...	...	4·2	4·3	4·2	...	...	...	Normal kidneys.
Mrs L. . .	...	...	2·6	2·6	...	...	...	...	Chronic interstitial nephritis.

Both tests would appear therefore to be ideal. But in my opinion Calvert's urea concentration range is immensely superior to the other. MacLean and de Wesselow apply their test during waking hours; Calvert's is applied when asleep, and it is well known that the concentrating power of the kidney is much greater by night. Therein, in my opinion, lies the superiority of the latter. MacLean and de Wesselow consider a concentration of 2 per cent. evidence of efficiency, yet the average daily urinary urea concentration is 2 per cent. If the daily demands on the kidney average 2 per cent. and if, according to Verney and others, only a few of the glomeruli are active at one time, can an ability to concentrate to 2 per cent. when the kidney is fully active be regarded as evidence of renal efficiency? It may mean there is evidence of sufficiency for daily needs, but the kidney cannot live up to this if it requires all its power, reserve included, to do it. Ability to concentrate to only 2 per cent. is, in my opinion, evidence of fairly advanced renal impairment; with the urea concentration range I have fixed the lowest maximum concentration for normal at 3·5 per cent. The difference in the result is entirely due to the technique employed.

Urea Concentration Range.

The test upon which the work reported now was done is the urea concentration range. The method was suggested by Calvert[5] in 1925, but no results obtained with it were recorded. At that time I was engaged in applying several of the aforementioned tests and along with these decided to try out the

urea concentration range. As no figures were available for it, the first necessity was to find the normal range and this was done by application of the test to over one hundred normal individuals. Thereafter it was applied to cases with known renal inefficiency and its results checked with the clinical findings and those of the other efficiency tests. So successful did it prove that now the other renal efficiency tests have been discarded, except in cases where doubt might appear to exist —where the urea range was apparently contradictory to the physical findings. Some such cases will be referred to later; and in all those quoted it will be seen that the range findings were eventually supported. The conclusions given are drawn from application of the test to about 700 cases.

Technique.—The technique of the test is comparatively simple and has been amended only slightly from that originally suggested by Calvert. From noon onwards on the day of the test, the intake of fluid is restricted as far as possible.* At 9 P.M. 15 grams urea in 100 c.c. water are given. Lest an initial urea diuresis should upset the result, the bladder is emptied at 10 P.M. From 10 P.M. to 6 A.M., with the patient asleep, the kidney concentration power should be at its highest, in view of the large amount of urea given and the associated fluid restriction. Consequently any urine passed during that time or when the bladder is emptied at 6 A.M. should contain the maximum concentration of urea the kidney is capable of passing. At 6 A.M., following the emptying of the bladder, 2 pints of fluid (usually 2 cups of tea and 1 pint of water) are given and the bladder emptied at 7 A.M. and 8 A.M., with a further specimen at 9 A.M. if a diuresis has not occurred. One of these specimens will show the minimum concentration of urea the kidney passes.

In all specimens passed the urea concentration was estimated and the specific gravity taken. In view of the number of tests being employed now where specific gravity is the only information required, it may be of importance to note that, while generally in agreement, the urea concentration was regarded as of greater reliability than the specific gravity. A range of specific gravity gave indication of efficiency or inefficiency but was less useful than urea concentration in grading the degree of any inefficiency.

Some emphasis requires to be laid on the necessity for fluid restriction preceding and during the test. Abnormally low maximum results in normal individuals were frequently found due to neglect of this point, the resultant increased output of

* The hours quoted were found most suitable in hospital practice but can be altered to suit the individual case.

urine giving a more dilute urea content. The large amount of fluid given at 6 A.M. might also be commented on here. It forms perhaps the one objection to the test, as 2 pints is a large amount of fluid to have to take on waking. Most patients manage it; if not, 30 oz. will prove sufficient in all except doubtful cases.

Normal Range.—The normal range was established following application to over one hundred individuals of all ages and both sexes. The highest maximum concentration found was 5 per cent., this being obtained in two patients (male and female). The minimum concentration in these was respectively 0·3 and 0·35 per cent. The youngest tested (aged 4) showed a range of maximum 4 per cent. and minimum 0·2 per cent., while the oldest (aged 83) showed 3·45 per cent. and 0·4 per cent. The results in all the normals in different decades are given in Table II. From this series of normal it was concluded that the lowest maximum concentration which was acceptable as evidence of full efficiency was 3·5 per cent., while similarly the normal minimum was fixed at less than 0·4 per cent. These figures are interesting when compared with the statement of Samson Wright[20] that "normal kidneys may concentrate to 4 per cent. or over." A typical normal range is given in Table III.

TABLE II.

Table showing Average Urea Range Figures over Varying Age Periods.

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 III.

Normal Urea Concentration Range.

Mrs S.—

A .	10 p.m.	6 oz.	1·4 per cent.
B1 .	10 p.m. to 6 a.m.	7 oz.	4 ,,
B2 .	6 a.m.	4 oz.	3·8 ,,
C1 .	7 a.m.	7 oz.	0·8 ,,
C2 .	8 a.m.	14 oz.	0·3 ,,

Maximum . 4 per cent. Minimum . 0·3 per cent.

Urea Concentration Range in Diagnosis of Renal Inefficiency.—The diagnosis of inefficiency was now easy in all cases showing a range outwith these established limits, but it was felt that to be entirely successful the test should be

capable of indicating the degree of departure from normal. In this too I feel success can be reported. It would appear that the first departure from normal consists in a fall of the maximum, the minimum at this stage remaining below 0·4 per cent. This minimum is probably accountable for either by a slightly higher concentration in the 7 A.M. urine or by a slight increase in the amount of urine passed during the night, both of these proving sufficient to evacuate all the urea. It was in this latter type of case that the restriction of fluid intake showed its importance. This first stage of inefficiency gave a

THE UREA CONCENTRATION RANGE.

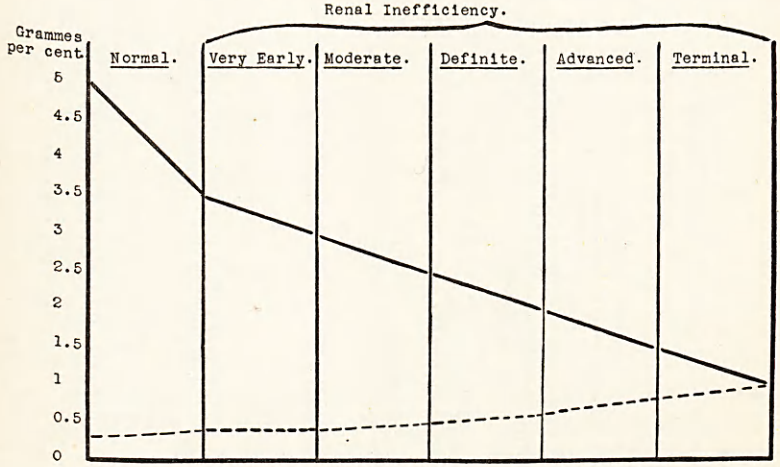


CHART 1.—Limiting values in normal individuals and in various stages of renal inefficiency.

Solid line—maximum; dotted line—minimum.

range of maximum 2·5 to 3·5 per cent. In the second stage the maximum ability to concentrate falls below 2·5 per cent. and is associated with a little retention of the urea given, showing itself by very slight rise of the minimum, *i.e.*, maximum 2 per cent. to 2·5 per cent., minimum 0·5 per cent. Fall of the maximum below 2 per cent. indicates a fairly severe degree of inefficiency and becomes associated with a higher minimum (0·6 to 0·8 per cent.). Thereafter, advancing inefficiency is marked by further approximation of maximum and minimum values until in the terminal cases the two values are practically similar. These results are recorded graphically in Charts 1 and 2.

Time does not permit of a résumé of the different groups of cases to which the test was applied. They are, however,

grouped in Table IV., which shows renal and non-renal conditions in which departure from normal is obtained and also renal conditions in which the test demonstrated that renal efficiency was normal. Many of the cases quoted were verified pathologically, and illustrative examples have been set out as a demonstration. Two of these demand brief reference. Both occurred in young people who were not suspected of renal impairment—blood pressure, heart, and retinæ, all being normal. The urea range demonstrated terminal inefficiency, the findings being verified pathologically in both cases within a month. In

THE UREA CONCENTRATION RANGE.

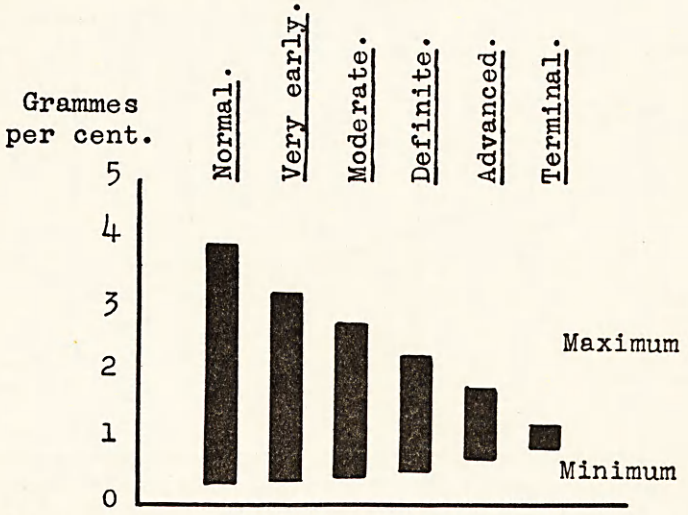


CHART 2.—Average values in normal individuals and in various stages of renal inefficiency, showing maximum and minimum values.

both cases other renal efficiency tests gave much less satisfactory information.

Two conditions noted on Table IV. require comment as possible fallacies in the diagnosis of chronic interstitial nephritis by the test. In both of these, renal inefficiency is shown to be present due to different causes—in cardiac failure, where renal congestion results in diminished concentration power, and in prostatic obstruction. In the latter it may be of surgical interest to note that information regarding the degree of renal inefficiency can be obtained in prostate cases, and also that following prostatectomy, in the few cases observed, a return to much higher values was obtained, indicating that opportune interference may result in considerable recovery of renal

efficiency. The ascertaining of renal inefficiency by the test may also prove valuable in determining the necessity for operative treatment.

TABLE IV.

Average Urea Concentration Range for Different Conditions.

Condition.	Average Maximum.	Average Minimum.
	Per cent.	Per cent.
Normal	3·5 to 4	0·4
Hyperpiesis	3·5 to 4	0·4
Chronic interstitial nephritis—		
Early	3	0·4
Moderate	2·5	0·45
Definite	2	0·5 to 0·6
Advanced	1·7	0·8 „ 0·9
Terminal	1·3 to 1·5	0·9 „ 1·2
Congenital cystic kidney	As for chronic interstitial nephritis	
Acute nephritis—		
Acute stage	0·9	0·65
Recovery	at least 3·5	0·4
Hæmaturia	3·75	0·4
Orthostatic albuminuria	3·6	0·3
Chronic parenchymatous nephritis	3·2	0·4
Nephrosis	4	0·4
Cardiac failure	2·5	0·5
Prostatic obstruction	1·7	0·7
(Varies with degree of inefficiency as for chronic interstitial nephritis)		
Other urinary conditions (pyelitis, oxaluria, etc.)	3·5 to 4	0·4

Urea Concentration Range in Prognosis.—The urea concentration range is useful in prognosis as well as in diagnosis. This is contrary to the opinion expressed by Beaumont and Dodds[3] "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 as to prognosis."

In high blood pressure with no renal lesion, the dangers are those of hæmorrhage, especially cerebral, cardiac failure, and intercurrent disease, the normal range showing that there is no danger of uræmia. In chronic interstitial nephritis and allied conditions, cerebral hæmorrhage and cardiac failure are grave dangers due to the high blood pressure, but ranking along with these in importance is the possibility of uræmia. The height of the diastolic pressure, the heart rate, and the appearance of extrasystoles, are helpful in the first two possibilities; in forecasting the probability of uræmia, the urea range is of equal importance.

As the degree of inefficiency increases the range decreases, and indicates uræmia is more imminent. In the initial stages a maximum of over 2 per cent. indicates that early uræmia

is unlikely; after the maximum falls below 2 per cent. expect uræmia within twelve months if the circulatory dangers do not previously intervene. A maximum below 1·5 per cent. with a minimum about 1 per cent. indicates an early uræmic termination. Urea is accepted as not the cause of uræmia, 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.

Several of the pathological specimens are illustrative of this prognostic aid; reference must be made to one as indicating how the progress towards uræmia can be noted by repeated application of the test.

K. M., female, aged 41 (at death).

1st Admission (12.11.26): Hæmatemesis; B.P. 170/100; blood urea 24 mgrms. per cent.; urea concentration range, max. 2·6 per cent., min. 0·4 per cent.

2nd Admission (21.2.30): B.P. 210/145; blood urea 45 mgrms. per cent.; urea concentration range, max. 1·7 per cent., min. 0·6 per cent.

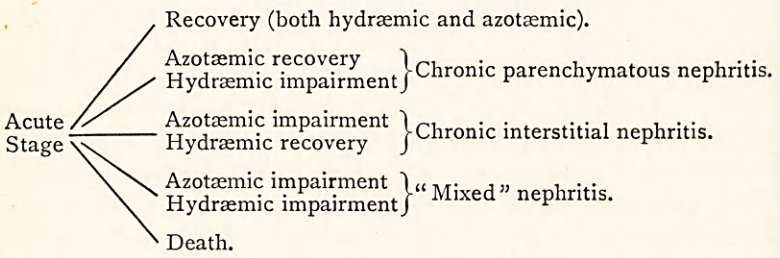
3rd Admission (23.7.30): B.P. 225/150; blood urea 84 mgrms. per cent.; urea concentration range, max. 1·4 per cent., min. 1 per cent.

Duodenal ulcer perforated while in ward. Died, seven days after operation, of uræmia, symptoms of which were present before perforation.

Post-mortem: Bilateral polycystic disease of kidneys; hypertrophy of left ventricle; duodenal ulcer.

In acute nephritis the prognosis may also be indicated by the test. The prognosis in this condition may be illustrated:—

Prognosis in Acute Nephritis.



The persistence of albuminuria and œdema directs ready attention to the possibility of chronic parenchymatous nephritis; scant attention is paid to the possibility of azotæmic impairment. Yet the degree of this damage can be ascertained by the urea range. In the early acute stage, the maximum is about 1 per cent. and minimum 0·6 per cent. With improvement the return towards normal can be observed, and no case should be con-

sidered as cured until the normal range has been obtained. Usually disappearance of albumin, casts, and œdema is the criterion of cure in acute nephritis; the azotæmic element, despite its greater importance, is forgotten. If the future is remembered, no case will be allowed up until the range is again normal.

The following case illustrates this point:—

J. C., aged 13.

8.4.31. Admitted with acute nephritis.
30.5.31. No œdema or albuminuria. Urea range—max. 2·4 per cent., min. 0·5 per cent.
1.7.31. Urea range—max. 3·3 per cent., min. 0·4 per cent.
14.7.31. Urea range—max. 3·5 per cent., min. 0·3 per cent. Allowed up.
16.10.31. Urea range—max. 4·3 per cent., min. 0·4 per cent.

My title covers the use of the test in diagnosis and prognosis only. It can be used also as a guide to treatment, but time forbids the inclusion of this in the present paper; it may be dealt with elsewhere later. The most important applications are in diagnosis and prognosis, and in these fields I feel the test has proved itself. I am satisfied to leave it to those of you who may care to apply it.

APPENDIX.

Illustrative cases shown in pathological demonstration:—

CASE I.—**Chronic parenchymatous nephritis.**

A. C., male, aged 31. Soakings at work three weeks before admission, followed by swelling of face and limbs. No previous history of throat trouble, scarlet fever or other exanthemata, nephritis, or tuberculosis.

Examination: B.P. 130/78. Early left ventricular hypertrophy.

Blood chemistry: Urea 43-79 mgrms. per cent.; creatinine 3-4 mgrms. per cent.; cholesterol 288-335 mgrms. per cent.; phosphorus 3·2 mgrms. per cent.; calcium 8·5 mgrms. per cent.; plasma proteins—albumin 1·66 gram. per cent., globulin 2·1 grams. per cent., fibrinogen 0·44 gram. per cent.; CO_2 combining power, 35 vol. per cent.

Urine: No blood; albumin 3 grams. per litre; granular casts.

Urea concentration range: max. 3·5 per cent., min. 0·4 per cent.

Post-mortem: Chronic tuberculosis, right lung; chronic parenchymatous nephritis.

CASE II.—**Hypernephroma.**

Mrs R., aged 52, admitted 30.9.32.

History: Four months prior to admission patient passed a quantity of blood-stained urine. This occurred again one week before admission. Two months prior to admission she noticed a lump in the left loin. This was painless. It progressively increased in size. Apart from slight weakness and some loss of weight she had no complaint.

Examination: Clinical and urological examination indicated a tumour of the left kidney. B.P. 145/95. Retinæ normal.

Blood chemistry: Urea 39 mgrms. per cent.; creatinine 3·0 mgrms. per cent.; cholesterol 155 mgrms. per cent.

Urea concentration range: max. 3 per cent., min. 0·3 per cent.

Operation: 10.10.32 (Mr Struthers). A large hypernephroma involving most of the left kidney was found. The tumour had burst through the capsule and was invading the diaphragm. Nephrectomy was performed.

Patient made an excellent immediate recovery from the operation, but she died five months later apparently of metastases. (No sectio.)

CASE III.—**Chronic interstitial nephritis.**

J. C., aged 19. Admitted semicomatose. No previous history.

Blood urea, 150 mgrms. per cent.

Urea concentration range: max. 1·4 per cent., min. 1·1 per cent.

Post-mortem: Typical chronic interstitial nephritis.

CASE IV.—**Chronic interstitial nephritis.**

C. S. M., male, aged 65, admitted 2.6.32.

History: Breathlessness on exertion for two months. Several attacks of intense nocturnal dyspnœa. One attack of pain in the chest suggestive of angina pectoris.

Previous history: Uneventful.

Examination: Small, thin, pale man. B.P. 240/150. Pronounced left ventricular hypertrophy. The retinæ showed changes indicative of "albuminuric retinitis."

Urine: Average quantity normal. 0·4 gr. per oz. of albumin (0·1 gram. per cent.).

Urea concentration range: max. 1·4 per cent., min. 0·8 per cent.

Blood chemistry:

Date.	Urea.	Creatinine.	Cholesterol.	Albumin.	Globulin.	Fibrinogen.	CO_2.
	Mgrms. per cent.	Mgrms. per cent.	Mgrms. per cent.	Grams per cent.	Grams per cent.	Grams per cent.	Vols. per cent.
3.6.32	85	4·7	196	...	...	...	62
18.6.32	70	3·8	120	...	...	...	46·5
22.6.32	63	4·0	140	3·57	3·25	0·54	45
27.6.32	125	4·0	115	...	...	...	46
13.7.32	370	4·2	130	...	...	...	30

27.6.32—Calcium, 10·07 mgrms. per cent.

Progress: From 20th June onwards his condition was that of chronic uræmia of slowly increasing severity. On two occasions the nocturnal dyspnœa was so severe as to necessitate venesection, which gave some relief. During his last week he had several copious bouts of melæna. Died on 16th July.

Post-mortem: Typical chronic interstitial nephritis; uræmic ulceration of cæcum; left ventricular hypertrophy.

CASE V.—**Chronic interstitial nephritis.**

Mrs B., aged 64, admitted 27.10.31.

History: For the year prior to admission patient had been troubled with breathlessness on exertion and swelling of the legs, this latter being worse at night. For twenty years patient had suffered from headaches and attacks of giddiness.

Previous History: Suffered from sore throats when she was young.

Examination: Cyanosed. Œdema of lower limbs. B.P. 230/150. Left ventricular hypertrophy. Retinæ showed extreme hypertensive retinopathy—"albuminuric retinitis."

Urine: Contained albumin, 2·5 gr. per oz. (0·6 gram. per cent. approx.).

Urea concentration range: max. 1·1 per cent., min. 0·8 per cent.

Blood chemistry: Urea 52 increasing to 212 mgrms. per cent.; creatinine 5·1 mgrms. per cent.; plasma albumin 2·75 grams. per cent.; plasma globulin 2·0 grams. per cent.; cholesterol 85 mgrm. per cent.

Progress: Condition gradually deteriorated. She showed signs of both uræmia and cardiac failure. Died 3.12.31.

Post-mortem: Kidneys showed typical chronic interstitial nephritis. Cardiac hypertrophy and dilatation.

CASE VI.—**Chronic interstitial nephritis.**

Mrs H., aged 30, admitted 23.4.31.

History: Vomiting and headache for last six weeks. Occasional diplopia.

Previous history: Uneventful except for gynecological operation one year prior to admission.

Examination: B.P. normal. No cardiac enlargement. Heavy albuminuria. Retinæ normal.

Blood: Non-protein nitrogen, 114 mgrms. per cent.

Urea concentration range: max. 1·2 per cent., min. 0·85 per cent.

Progress: After slight temporary improvement she gradually became worse and died on 31.5.31.

Post-mortem: Kidneys showed typical chronic interstitial nephritis. No cardiac hypertrophy.

Note the absence of hypertension, a rare and interesting phenomenon.

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Discussion.

Dr J. D. Comrie said—I agree with Dr Cameron that the overwhelming advantage of this urea concentration method is that it is so easy for the doctor, and also for the patient, and can be carried out simply and with reliance on its exactitude. At the same time, however, I should like to say a word for the other tests. I believe that the dye test, introduced by Rowntree—the injection of phenolsulphonephthalein—is a valuable test, as a check upon the urea concentration test, and I think that the best of all tests is the estimation of urea in the blood. It has, however, the great disadvantage, as Dr Cameron pointed out, that it cannot be carried out by the doctor, and the specimens must be sent to a laboratory. At the same time, I think one can draw definite conclusions in regard to prognosis from variations in the increase of blood urea, each rise to 50, 60, 80, 100, or 120 mgrms. giving a definite prognostic indication, so that I think the blood urea test is really the most satisfactory for information, although for the practitioner it has this inherent difficulty. With regard to the urea concentration range, Dr Cameron has taken great interest in this particular way of making the test, namely, estimating the range between the maximum and the minimum concentration, but I am not quite convinced that it is really essential to get the minimum concentration. If one is content with the maximum, one can draw pretty nearly the same conclusions. I thought so as I looked at the admirable charts Dr Cameron showed. MacLean, some years ago, at a meeting of the British Medical Association, introduced his test, and I agree with Dr Cameron that when Dr MacLean said he was content with a maximum concentration of 2 or 2·5 per cent., after the administration of 15 grams. of urea, the figure was really far too low. I pointed out at that time that in Scotland most normal people concentrated up to 3 or 4 per cent., and

that was off-set by a man from Devonshire who pointed out that in his part of the country the normal individual concentrated up to 5 or 6 per cent. I think that Dr Cameron is right in not being satisfied with less than from 3 to 4 per cent., but, with all due deference to him, I am not convinced that one must necessarily estimate the minimum concentration.

Mr Henry Wade said the exact estimation of renal functional activity is not only of importance to the physician but also to the surgeon. To those of us who especially have to deal with lesions of the urinary tract, it is not merely of importance, it is of vital moment, as in so many of our cases renal functional activity is seriously impaired, and according to the estimation made of the degree of the damage, the form of treatment to be employed will be determined. As is generally recognised, it is in prostatic surgery that this is especially the case, for there, according to the estimated damage to the kidneys, the operation will be carried out in one or two stages. In the wards under my charge in the Edinburgh Royal Infirmary we have employed in a somewhat modified form the method described by Dr Cameron, and we have found it undoubtedly to be the most delicate test available for estimating renal function. The difficulty in carrying it through is to be found more in the labour it entails: in a surgical ward where a busy waiting-day comes once a week it is sometimes not so easy to have the co-operation of the house surgeon and nursing staff to carry it through in the manner proposed. It may be, therefore, for this reason that we employ more widely the blood examination—estimating the blood urea, non-protein nitrogen, and creatinine—and we find it in most cases a very efficient guide, combined with other information obtained. In the advanced case of prostatic retention, of course, the urea concentration range test would not be possible owing to the inadvisability of emptying the bladder completely, which would not only tend to invalidate the accuracy of the findings but would also to a certain extent endanger the patient's life. Speaking for the surgical side of the House, I should like to assure Dr Cameron how much we appreciate his work, and to tell him that he will find no finer physiological laboratory than the surgical operating theatre. He will find there cases that will well repay his further investigation, and we would cordially welcome his co-operation.

Dr J. G. M. Hamilton said—Dr Cameron laid great stress on the fact that the Calvert urea concentration range gave figures in what he considered to be abnormal patients, which would have been disregarded by MacLean as being what he considered normal, but I think perhaps he did not stress quite sufficiently the difference in technique between the two tests. At an early stage of his paper he told us that MacLean's test was carried out through the day, while Calvert's test was carried out during the night. It would have been of considerable interest if Dr Cameron had shown a comparison between Calvert's urea concentration range and MacLean's urea con-

centration test, so that one could have seen whether there actually was the fallacy he alleged was present in MacLean's test, in that the latter had not taken high enough readings. One agrees, of course, with Dr Comrie, that the minimum adopted by MacLean for normality is probably too low, but that is the standard laid down by MacLean, and one would have liked to see the results which MacLean's test actually gave in some of Dr Cameron's patients.

Mr David Band said—During this winter I have been applying the urea concentration range test to some half-dozen cases of prostatic retention. There the difficulties in carrying out the test were, of course, retention of urine, and that the patients had to be catheterised while the test was being done. It was arranged to commence the test at midnight so that further catheterisation was not required until 8 A.M. One or two cases were investigated with indwelling catheters shortly after admission to the ward. I grant there was a risk, but one was very anxious, with due precautions, to test out the method. One interesting result thus obtained was that in some cases the "minimum" has been very high—in one or two cases the second specimen which should have shown the smaller reading, gave one which exceeded that of the first specimen, which should have been the "maximum." The trouble is that when drainage is commenced following retention of urine there is a period of a few days during which the urine is diminished in amount, even in spite of forced fluid intake, and, in certain cases, that may go on to anuria, leading to death. As Mr Wade has just indicated, that is what has been the fear of every surgeon dealing with the distended bladder, and one wonders whether there is not always considerable congestion of the kidney immediately after drainage is established. I should like Dr Cameron to consider whether, in carrying out these tests, with catheterisation, the raised minimum reading has not been due to congestion in the kidney leading to a false concentration power during the period of the test. The patients on whom the test has been carried out have all done well, although their readings were so adverse, when compared with Dr Cameron's figures. One goes back to the time when uroselectan was first used, and when Mr Wade and I were investigating the renal secretion rate of uroselectan. In cases of prostatism with retention in that series we noted that there was delayed secretion of uroselectan, as a result of impairment of function; but if the actual amount secreted was sufficiently high, might it be that the patient appeared to have an adequate renal reserve. A high minimum reading having been obtained in a prostatic patient by the urea range test, we are dealing not with a severely defective kidney but with a kidney which is damaged but which has reserve and which, if given the opportunity, will respond and carry the patient through his operative treatment.

Dr Fergus Hewat said—I have tested a considerable number of high blood pressure patients by blood urea estimation—from which I

did not get very much help—and by the MacLean and de Wesselow concentration test—from which I have got a great deal of help. Like Dr Hamilton, I should like Dr Cameron to tell us something about comparative readings between these two tests—Calvert's and MacLean's —in similar people, and show us whether there is relative coincidence or not. Dr Cameron mentioned the fact that Calvert had no normal figures to give as a basis. On what then was the test based? The final point about which I should like a little help is in connection with high blood pressure cases. One sees so many people with high blood pressure, who, one suspects, have commencing kidney trouble, but cannot quite prove it by functional tests. One wonders whether Dr Cameron could get a certain amount of that doubtful high pressure group into what one might term a true renal group by the Calvert test. I have seen several patients who have had high blood pressure for years without any very gross urinary disturbance, and certainly no blood urea deficiency until terminally, and yet they have all died of uræmia.

Dr J. D. S. Cameron, in reply, said—In replying to the criticism that has been offered I think it might be preferable to take one or two points which have been generally raised by several speakers. First, as to the value of the blood urea test. I feel that the estimation of the blood urea is of value in the terminal stages of the case, when very definite renal inefficiency has been already diagnosed. I do not think the value of Calvert's test lies in such cases. I am not putting forward this test as merely of value in diagnosing the terminal cases of renal inefficiency: the importance I attach to it is the diagnosis of renal inefficiency in the very early stages. I think that for far too long we have been content to say there is no renal inefficiency until the symptoms of polyuria, etc., appear. I venture to suggest that there is a wide gap between the normal and the stage at which such symptoms appear, and it is in that gap that I think the urea concentration range is of value, long before the time when the blood urea can be expected to rise. I think the blood urea estimation will prove of value when renal inefficiency is far advanced.

Dr Comrie raised the point as to the use of the minimum reading. Originally I saw little use in estimating the minimum, but gradually I have come to consider that the estimation of the minimum allows us to do without estimation of the blood urea. I think it can be taken as fairly well established that, so long as there is no rise in the minimum concentration, there will be no rise found in the blood urea, and it is only when the minimum begins to rise that increase in blood urea is to be expected.

Dr Hamilton and Dr Hewat raised the question of a comparison between Calvert's method and the method of MacLean and de Wesselow. At one time I had the feeling that my paper was going to consist entirely of introduction, and I did not wish to be too long in getting to the point. That is the only reason I can offer as my excuse for not giving such a comparison. I might point out that MacLean's concentra-

tion test was done for a long time along with Calvert's urea concentration range, and I think that in the most advanced cases we did get information from the MacLean method, but it was not nearly so valuable in determining the early cases. For example, the case of polycystic disease which was quoted showed at first a urea concentration range of maximum 2·6 per cent. With the Calvert method, that implied renal inefficiency, while according to the MacLean method the condition of that patient was normal. The subsequent progress of the case is, I think, sufficient justification for adopting Calvert's test in preference to MacLean's.

Dr Hewat asked why Calvert suggested the test, if he did not give any normal figures. Calvert originally suggested the test in a very short article in the *British Medical Journal*, expressing his extreme dissatisfaction with the test of MacLean and de Wesselow, and suggesting that the reason for this dissatisfaction might be because the test was applied by day. He therefore wondered whether applying the test by night might not give a better result.

Dr Hewat also inquired about high blood pressure cases. I find there are quite a number of high pressure cases in which the normal range of urea concentration is obtained, but these are individuals showing no evidence of renal inefficiency, even though the test is repeated on more than one occasion. I can recall one patient with high blood pressure who has been tested repeatedly during the last three years, and she is still showing no evidence of renal inefficiency.

With regard to the surgical queries brought up by Mr Wade and Mr Band, these are, to me, extremely interesting, and I am pleased that Mr Band is applying the test to such cases as he described. I confess to feeling that my own experience of prostatic cases has been far too limited. I have given you notes of the application of the test to over 700 cases, but unfortunately only about 20 were prostatic cases. I have probably been remiss in not applying the test in more of these cases, but I am merely throwing out the suggestion that such a test might be of value, first, before prostatectomy, and secondly, in determining the amount of functional recovery which is effected.

In connection with the blood urea estimation, there is a point about the actual taking off of the blood which is rather important. It is quite easy to take off blood in hospital and send it to a laboratory, but I doubt if such a course is acceptable to the general practitioner.

In regard to the last point raised by Mr Band, regarding uroselectan, I think Mr Band will recall co-operating with me in one case of uræmia. In that case there was a very slight secretion of uroselectan and the urea concentration range test suggested a terminal stage of chronic interstitial nephritis with no cardiovascular involvement.