AN INVESTIGATION INTO THE EFFECTS OF WAR NEPHRITIS ON KIDNEY FUNCTION, WITH OBSERVATIONS ON METHODS FOR ESTIMATING THE EFFICIENCY OF THE KIDNEYS

(A Report to the Medical Research Committee)

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CONTENTS.

I. *Methods of Investigation.*

- (1) Urea and non-protein nitrogen in blood.
- (2) Diastatic index of urine.
- (3) Concentration of urea in urine and urea test.
- (4) Chloride content of urine.

II. *The Effect of War Nephritis on Kidney Function.*

- (1) Azotaemic type of war nephritis.
- (2) Hydraemic type of war nephritis.
- (3) Illustrative cases showing azotaemic, hydraemic, and mixed types.

III. *Observations on Treatment.*

- (1) Diet in azotaemic type.
- (2) Diet in hydraemic type.
- (3) The effect of large protein diet in removing ascites in chronic parenchymatous nephritis.
- (4) The effect of urea in causing diuresis in nephritis.
- (5) General observations on protein diet in nephritis.

IV. *Discussion of Tests for indicating Kidney Efficiency.*

- (1) Blood urea, diastatic and urea tests.
- (2) Phenolsulphonephthalein.

THE present paper deals with certain observations on nephritis cases carried out at No. 5 Military Hospital, London. The laboratory conditions here were naturally much better suited for the investigation of this type of disease than was the case in France, and we were enabled to carry out observations on individual patients extending over a period of several months. The chief points on which information was sought were the interpretation of certain tests and the effects of the disease on the kidney function as indicated by the retention of metabolic products.

Our intention was to endeavour to obtain some idea as to the probable prognosis—both immediate and remote—in these patients, and from this point of view the cases were subjected to a thorough examination at frequent intervals.

I. Methods of Investigation.

Various tests which will be referred to later were used from time to time, but, since the following methods were found to give the most valuable results in our hands, a short discussion of them at the present stage will render clearer various subsequent statements and save repetition.

In our experience the most useful chemical tests are found to be—

- (1) Estimation of the concentration of urea and non-protein nitrogen in the blood.
- (2) The diastatic content of the urine.
- (3) The concentration of urea in the urine after giving a dose of urea by mouth.
- (4) The chloride content of the urine.

Blood urea in Nephritis. One of the most valuable tests we possess for determining the extent of renal inefficiency in a given case of nephritis is the estimation of urea in the patient's blood. In a normal individual, on an average mixed diet, the blood contains from 20 to 40 mg. urea per 100 c.c. of blood. When the renal function begins to fail, a point is reached at which it becomes difficult for the kidney to deal with the urea and other nitrogenous waste products, with the result that the amount of these bodies in the blood tends to increase. With an increased concentration of urea in the blood, the diseased kidney is able to pass as much urea as the normal kidney, so that nitrogenous equilibrium is still maintained.

Thus, it generally happens that, even in a severe case of chronic Bright's disease, the average amount of urea excreted *per diem* is exactly the same as that passed by the normal individual on a similar diet.

The essential difference between the two cases is that in the healthy person the urea is excreted from blood containing the normal amount of urea, while in the nephritic the blood contains excess of urea.

The reason for this need not be discussed here, but it is obvious that if the excretion of urea depends on filtration of the non-colloidal liquid part of the blood through the glomerulus of the kidney, then the greater the concentration of urea per unit of blood, the larger will be the amount of urea passing through into the kidney tubules.

We may also look at this from the point of view of F. C. MacLean (1), who considers that the stimulus required for the excretion of urea in the healthy kidney is furnished by a concentration of 20 to 40 mg. per 100 c.c. blood, but that it requires the stimulus of a higher concentration of blood urea to give the same result in a diseased kidney. Another important factor in the maintenance of nitrogenous equilibrium is the passage of an increased amount of water.

At any rate, it is quite obvious that in many cases the diseased kidney must be able to eliminate the total amount of urea and other nitrogenous products formed in the body, otherwise there would soon be a very much greater concentration of these substances in the organism than is found to be the case.

In short, the chronic nephritic in general eliminates the usual 30 grm. or so of urea per day, just as the healthy individual does, but, while the blood of the latter usually contains less than 40 mg. per 100 c.c., the former may have a concentration of 100 mg. per 100 c.c. or much more.

From this it is evident that no information is to be obtained in an ordinary chronic case of nephritis by estimating the daily amount of urea passed in the urine, for this will depend chiefly on the amount of protein ingested and not on the condition of the kidney. Much information may, however, be derived from an examination of the blood, and it is unfortunate that the teaching at present in vogue to the effect that urea *per se*, even in large amount, produces no deleterious effects on the body, is often accepted as indicating that the amount of urea present in the blood is of no clinical importance. Whether or not urea acts as a toxic substance when present in high concentration is at present unsettled (2), but that the amount of this product present in the blood furnishes us with an excellent index of the efficiency of the kidney is undoubted.

Generally speaking, the other non-protein constituents of the blood (uric acid, kreatinin, purin bodies, &c.) are found to vary roughly with the urea, so that the same information is obtained by estimating the total amount of non-protein nitrogen in the blood. As the estimation of urea is a much simpler and shorter process, it is best adapted for clinical work, and though we have made a considerable number of estimations of non-protein nitrogen in nephritis cases, we have not been able to obtain any clinical information by this method which was not furnished by the simpler plan of estimating the urea alone.

Since we all possess renal tissue largely in excess of the requirements of the body, it follows that the kidneys may suffer considerable damage and yet sufficient renal substance remain to carry on the normal functions of this organ in the usual way. In such a case, no indication of renal inadequacy would be obtained by estimating the blood urea, for the latter would not be increased. When, however, the available tissue is just insufficient to maintain nitrogenous equilibrium with a normal blood urea concentration, the blood urea immediately goes up in proportion to the extent of the kidney lesion.

When the damage to the kidney is insufficient to produce an increase in the blood urea, evidence of inadequate function can be obtained by other tests to be described later.

In recent acute cases of nephritis there is generally some retention of urea if the condition is at all severe, and the blood may show from 50 to 600 mg. per 100 c.c. or even more. In mild cases there is a gradual return to normal, the rate at which this takes place depending on the severity of the condition. In unfavourable cases, on the other hand, the concentration tends to increase, and in such patients the prognosis is often bad in spite of a favourable clinical condition. In a few of our acute cases in which the urea attained a concentration of 250 to 300 mg. apparently complete recovery took place, but in every instance in which the amount exceeded 300 mg. death ensued. In two such fatal cases the first estimation gave a result of about 200 mg. per 100 c.c. blood, but this amount

steadily increased until the blood contained 600 mg. At this point death took place in both. It is worth noting that in neither of these patients did the clinical condition and general appearance give any indication of the gravity of the condition until a few days before death, and, except for the persistent increase of blood urea, a favourable prognosis might have been given.

Though there is a tendency to retention of urea in practically all cases of acute nephritis, this is by no means true of all chronic cases. In this respect there is a very marked difference between the cirrhotic variety of Bright's disease and the true parenchymatous entity. In the latter, as will be fully discussed later, there is little or no tendency for urea to be increased in the blood, while the former often shows this condition to a very marked extent.

Method of estimating urea in blood. The estimation of blood urea was carried out by the well-known urease method on the lines described by Van Slyke (3). Instead of using a specially prepared enzyme we made use of finely-ground soya bean meal, which is easily prepared at any time. To 3 c.c. of blood in a suitable test-tube 0.3 gm. of bean meal was added, and the closed tube placed in a water bath at 37° C. for fifteen minutes. Before distilling off the ammonia formed, 4 c.c. of a saturated solution of potassium carbonate, together with 3 gm. of solid anhydrous potassium carbonate, were added to the tube containing the blood. This was found to give a medium of suitable consistency for the passage of the necessary current of air. As an indicator, one drop of a saturated solution of methyl red in 50 per cent. alcohol was employed. In all other respects we followed the directions given by Van Slyke.

The use of soya bean meal simplifies the procedure very materially as the commercial enzyme preparation is not always easy to procure in this country. The meal has the further advantage that it retains its activity unaltered for several months, while the commercial enzyme tends to deteriorate very quickly. The meal yields a small trace of ammonia, which must be allowed for in very exact work. As the result of many experiments it was found that all our samples gave practically identical values under the conditions of the experiment, 0.3 gm. of the ground bean yielding ammonia equivalent to 0.4 c.c. of N/100 acid.

To prevent frothing there is nothing so efficacious as secondary octyl alcohol, and though other preparations have been recommended from time to time they have not yielded entirely satisfactory results in our hands.

The diastase of urine and the diastatic test. Though the presence in the urine of a ferment capable of hydrolysing starch was known for a long time it was not until 1908, when Wohlgemuth (4) devised a method for its quantitative estimation, that any attention was paid to the matter from the clinical standpoint. Wohlgemuth, however, recognized that the amount of this substance in the urine was fairly constant, provided the kidneys were acting efficiently, but that diseased kidneys failed to excrete it in normal amount. Since this observation was made, many papers have been written on the subject, the general consensus of opinion being that there is undoubtedly a marked decrease of this ferment in the urine of individuals suffering from nephritis, especially of the chronic interstitial variety.

Like every other test, the diastatic test suffers from certain drawbacks, and cannot of itself be always relied upon to indicate the renal condition. On the other hand, it is, in our opinion, a most valuable aid when used in conjunction with other methods. No doubt, there are healthy subjects in whose urine the diastatic value occasionally varies considerably from the normal, but from an experience of the test extending over six years we have come to the conclusion that some of the difficulties that are supposed to be associated with it are grossly exaggerated. There is little doubt that the average amount of diastase in the urine of the healthy individual is extraordinarily constant within comparatively narrow limits, and it is rare to get values in healthy subjects either below or above the numbers given below. In rare instances where the results are abnormally high some explanation is usually forthcoming if the case is carefully investigated.

Technique employed. As the technique of the test is apparently not very well known in this country, details of the method are given here. The following solutions are required:

(1) A 0.1 solution of 'soluble' starch in distilled water. Since different solutions of 'soluble' starch vary in the rapidity with which they are hydrolysed by diastase, it is quite possible that different samples of starch would yield different results with urine. To avoid this error it is necessary to test a new sample of starch with several specimens of average healthy urine. By this means the action of normal urine on any particular specimen of starch can be ascertained. When this is once known there is no further trouble, as the starch does not apparently change on keeping. To avoid the necessity of control experiments it is well to procure a sufficient amount of starch to begin with, and always use the same sample. Generally, specimens of soluble starch manufactured by any of the firms dealing in fine chemicals, will be found satisfactory.¹ The solution should be prepared fresh, as after a few days it deteriorates and is then useless.

(2) A sodium chloride solution of about 1 per cent. strength.

(3) A solution of iodine of about 0.5 per cent. strength.

For the test from 3 to 5 c.c. of urine are required. For an average urine ten test-tubes of equal size are taken, and to each are added decreasing amounts of the urine from 0.6 c.c. to 0.06 c.c. The total volume in each tube is then made up to 1 c.c. by the addition of sodium chloride, and finally 2 c.c. of the starch solution are added to each. The amounts of the different liquids required are as follows. The d values corresponding to the final readings are given in the last column.

¹ At first we employed Kahlbaum's starch, but since 1914 we have used a specimen prepared by Messrs. Baird and Tatlock which gives almost the same results as the German preparation.

TABLE I.

Number of Tube.	Amount of Urine in c.c. in each Tube.	Sodium Chloride added to each Tube in c.c.	Starch Solution added to each Tube in c.c.	Corresponding <i>d</i> Value.
1	0.6	0.4	2	3.3
2	0.5	0.5	2	4
3	0.4	0.6	2	5
4	0.3	0.7	2	6.6
5	0.2	0.8	2	10
6	0.1	0.9	2	20
7	0.09 = 0.9 c.c. (dil. 1 in 10)	0.1	2	22
8	0.08 = 0.8 c.c. „	0.2	2	25
9	0.07 = 0.7 c.c. „	0.3	2	28
10	0.06 = 0.6 c.c. „	0.4	2	33

For measuring the urine a 1 c.c. pipette divided into hundredths is required. By this means quantities from 0.6 to 0.1 c.c. can be measured directly; for the smaller amounts it is necessary to dilute the urine in the proportion of 1 part urine to 9 parts salt solution and take corresponding amounts of this. For adding the saline solution a small 10 c.c. burette is most convenient, while the starch solution is best added from a 25 c.c. burette.

When all the tubes are ready they are quickly shaken and placed in a water bath at 37° C. for exactly thirty minutes. They are then taken out and nearly filled with cold distilled water to stop the ferment action. One drop of iodine solution is added to each tube, and starting from No. 1, note is taken of the first tube in which a blue tint is observed. This tube contains just that amount of urine which failed to convert all the starch into dextrin under the conditions of the test. The tube next to this, which may be clear or show a reddish tint, is taken as the 'limit', and from this tube the diastatic value is calculated. This so-called *d* value is empirically expressed in units, and represents the number of cubic centimetres of 0.1 per cent. 'soluble' starch solution which the particular urine is capable of digesting in half an hour at 37° C. This value is obtained by dividing the number of cubic centimetres of starch solution used (2 c.c.) by the amount of urine required to digest this amount of starch. For instance, if the necessary quantity of urine was 0.1 c.c., then the diastatic value = 20. For the tubes containing a relatively large amount of urine more than 1 drop of iodine solution will be required, but the necessary amount is soon ascertained by a little practice. At first, it is not always easy to be quite certain which of two adjacent tubes should be taken as representing the limit, but this is of little importance in practice, for what we really want to know is whether the urine is low in diastase, and this is easily ascertained. Very exact readings are unnecessary for clinical work, and it is not essential to put up all the tubes given in the table.

In the healthy the *d* value varies from 6.6 to 30, the average generally being from 10 to 25. It varies to some extent at different times of the day, and on this account it is best whenever possible to test a sample from the total twenty-four hours' urinary output. Corbett (5), who used the test extensively, never found

a higher value than 40 in a healthy individual. Generally speaking, a constant value below 6.6 may be taken to indicate a defective kidney, provided some other condition is not present in the body by which the diastatic content of the blood is lowered. The average d value of the plasma appears to be between 5 and 10. In a series of fifty-one cases, including normal and nephritic subjects, the following figures were obtained for the plasma :

8 patients =	.	.	.	.	.	5 d value
24 „ =	.	.	.	.	.	6 „
18 „ =	.	.	.	.	.	10 „
1 „ =	.	.	.	.	.	28 „

In the class of nephritis cases in which diastase tends to be retained one expects a value below 6.6 in the urine, and the lower this value is the more serious appears to be the condition of the kidney. We have not yet seen in any subacute cases a high diastatic value associated with a tendency to nitrogenous retention. During the early acute stage of nephritis this test may be normal, as it was in one fatal case. Here, however, the blood value was 28, so that the normal kidney would be expected to give a much higher value than the $d = 10$ actually found. In some nephritics the diastatic value gradually gets less as convalescence proceeds, and in such cases evidence of progressive degeneration can usually be obtained by other tests. As a rule, it is more or less normal in chronic parenchymatous cases, but is often very low in the interstitial variety of nephritis. In our experience, a patient with a very low diastatic value during the early acute period of the disease does not usually do well, and it is possible that such patients may be suffering from some slight chronic mischief. The results obtained by this test in our cases are given later.

The concentration of urea in the urine. From what has been already stated it is clear that no results of value can be expected from estimations of the daily output of urea in chronic nephritis. In the early stages of acute cases there is undoubtedly a marked decrease in the amount of urea passed, but this generally lasts only for a few days, during which time there is a corresponding increase of nitrogenous waste products in the blood and tissues (6). In the subsequent course of certain of these cases a condition is gradually established in which the concentration of urea in the urine is much less than the usually accepted amount. Average urine from a healthy individual on ordinary mixed diet is held to contain roughly about 2 per cent. urea, but it is certain that this figure is too high ; in our experience the average for hospital patients with sound kidneys is nearer to 1.6 per cent. than 2 per cent. In nephritics in whom there is a tendency to retain nitrogen, the power of concentration tends to be diminished, a condition well recognized in chronic interstitial disease. This also takes place during convalescence from acute nephritis, and appears to indicate that the kidneys are still suffering from what in some cases must be a progressive form of disease, though ultimate recovery appears to be possible. This loss of power to concentrate urea may not be easily detected in ordinary specimens of urine, but can be readily

brought out by giving the patient from 15 to 20 gm. of urea in a little water and estimating the percentage of urea in the urine passed some time afterwards. This test has been found to give most valuable help in arriving at a conclusion as to the efficiency of the kidneys.

Experiments were first made to determine whether cases with urea retention could be distinguished from those in which the blood urea was within normal limits by differences in the *total amount* of urea passed in a given time after a dose of 10 or 15 gm. The bladder having been emptied, the patient received the dose of urea dissolved in 400 c.c. of water; the bladder was again emptied 4 hours later. In some cases the amount of urea passed in the hour preceding the dose was determined, and from this the 'excess' urea passed in the four hours following the dose calculated. This method failed entirely to differentiate between those patients in whom the blood urea was known to be above the normal and those in whom no such retention had been observed. It was, however, noticed that the *concentration* of urea in the urine after the dose appeared to bear a definite relationship to the severity of the case, patients with urea retention passing a relatively large amount of urine, with a low urea concentration, while patients without retention passed smaller amounts of urine, but concentrated to a considerably higher figure. In patients in whom there had been persistent urea retention, but whose blood at the time of the test showed normal values (presumably cases in which the kidney tissue was considerably damaged), the concentration was lower than was found in patients with little or no earlier retention.

With a view to bringing out this apparent difference of concentrating power and arriving at an estimate of the functional capacity of the kidney as regards urea concentration, the following test was applied to a series of cases. The patient took no food or drink after 7 p.m.; at 6 a.m. he emptied his bladder and received a dose of 15 gm. of urea dissolved in 100 c.c. of water. At 8 a.m. the bladder was again emptied and the concentration of urea in this specimen of urine estimated. The fluids were purposely limited, and the urea dissolved in a small amount of water with a view to producing a maximum urea concentration.

The results of this test in a series of convalescent cases of nephritis are given in the following table. Blood urea concentration and values are included for purposes of comparison. In a series of normal cases the concentration varied from 2 to 3.5 per cent.

TABLE II.

Number.	Nature of Case.	Urea % (2 hours specimen).	Urine (amount in 2 hours) in c.c.	Blood Urea Concentra- tion in mg. per 100 c.c. Blood.	d Value in specimen from 24 hours' Urine.
1	Cases of nephritis in which	2.46	117	34	6.6
2	no retention had been	2.07	121	27	10
3	observed	2.54	80	20	10
4	"	2.93	108	25	5
5	"	2.14	147	30	6.6
6	"	2.38	108	24	6.6
7	"	2.67	127	24	5
8	"	2.07	132	34	5
9	"	2.58	113	31	6.6
10	"	2.50	114	36	2.5
11	"	2.22	126	36	5
12	"	2.16	153	33	6.6
13	Cases in which slight reten-	1.43	180	28	2.5
14	tion had been present a	2.07	132	34	5
15	few months earlier	1.89	145	39	2.2
16	Cases with retention	1.55	167	44	1.4
17	"	1.54	258	41	3.3
18	"	1.46	235	48	4
19	"	1.27	235	58	< 1
20	"	1.09	187	52	1.2
21	"	1.13	379	74	< 1

In a number of these cases the test was carried out on several occasions. The results on the whole were concordant, and it is not improbable that some of the slight differences in concentration found on repeating the test after an interval indicated actual changes in renal efficiency, for such differences were generally accompanied by corresponding changes in the diastatic index. In a few instances, a kidney which had previously shown good concentration yielded on re-testing an abundant urine with a low concentration, though no obvious change in the patient's condition had taken place. Without exception, however, the concentration in the cases in which urea retention was present remained low. In such cases a genuine inability to concentrate urea appeared to be present. While, therefore, a high concentration on testing appeared to indicate kidney efficiency, occasionally excessive diuresis and a low concentration were seen in cases in which the kidney function was apparently not seriously affected. This phenomenon is a result of the tendency to diuresis caused by the urea in the presence of available liquid, and may be overcome by waiting for a specimen of urine until this normal diuresis passes over. In general, if the amount of water passed per hour does not greatly exceed 100 c.c. or so, the difficulty does not arise. On the whole, since it is in practice difficult to regulate the amount of water available in the body, it is best to empty the bladder two hours after the urea is given and to examine the next specimen passed, say, in one half or one hour. Thus, if a patient gets 15 grm. of urea at 10 a.m., he should pass water at 12 a.m. If a large quantity is passed at this time and it is found to be low in urea, a further specimen should be passed about 1 p.m. This later specimen may be taken as an indication of the urea concentrating power of the kidney, since the normal

diuresis appears to be limited to the early hours after the ingestion of urea. Persistent diuresis for several hours appears to indicate defective kidneys.

The chloride content of the urine. It is sometimes forgotten that the function of the kidney is not restricted to the elimination of waste products. This gland fulfils another very important office in regulating the concentration of salts in the plasma. MacAllum (7) in a very interesting paper has shown that the salt content of plasma was probably determined originally by the salt content of sea-water, the medium in which all life had its origin.

Of the salts of the plasma the chlorides are the most easily estimated, and since the bulk of these salts is represented by sodium chloride the chloride content of both blood and urine is generally expressed in terms of sodium chloride. This practice is of course not scientifically correct, but gives sufficient accuracy for clinical purposes.

In certain cases of nephritis associated with oedema there is undoubtedly a tendency for the excretion of chlorides in the urine to be diminished; in some instances, indeed, they may be absent. Much discussion has taken place over the question whether this decrease in urinary chlorides is primarily due to a specific defect on the part of the kidney to eliminate salt, or whether it results from retention of water in the organism. From the practical point of view the result is the same. If we remember that any marked change in salt concentration in the fluids of the body is incompatible with life, it is evident that if the body retains fluid it will also retain salt in amount sufficient to form a solution of optimum concentration for cell activity: this concentration corresponds roughly to a 0.6 per cent. of sodium chloride solution.

If, on the other hand, salt is specifically retained, this will immediately lead to a retention of water in order to prevent excessive salt concentration in the body. It is one of the functions of the kidney to keep the concentration of chlorides in the plasma in the neighbourhood of a 0.6 per cent. solution. Unlike urea and other bodies which appear in greater percentage in the blood when the kidney fails to eliminate them, salt does not do so. In patients passing practically no salt in the urine, the blood salt concentration is little if at all higher than is the case in the healthy individual who may be passing 15 gm. per day. It is highly probable that in some conditions the kidney cells have really lost the power to eliminate chloride in the normal manner, for chloride retention is by no means always associated with a small output of water. In other cases, the phenomenon may be the result of a diminished power to excrete water, with consequent reabsorption of salt by the renal tubules. In the first case there appears to be a tendency for the patient's blood to contain chlorides in the maximum normal concentration, but such a concentration is not materially above the normal minimum concentration and may be reached by healthy individuals. Roughly speaking, the variations of salt concentration in the plasma range from about 0.55 per cent. to about 0.63 per cent.

There appears to be some evidence that a persistent low blood chloride concentration in a case of nephritis indicates primary water retention, while the

reverse condition suggests a primary salt retention. This view seems to be borne out by some experiments made by us, but we have not had sufficient cases to enable us to make any definite statement and so must leave the question an open one.

It is by no means a simple matter to determine whether a nephritic has any tendency to salt retention. The general method employed is to give a large dose of 10 to 15 gm. of sodium chloride by mouth and then estimate the amount passed in the urine. Unfortunately, such a method does not appear to give any reliable information, for, according to various investigations carried out by French observers and other authorities, the ingestion of a large amount of salt does not necessarily mean that an equivalent amount should be excreted by a healthy individual. According to Vallery-Radot (8), for instance, the amount of salt excreted after a given dose depends on the state of the tissues with regard to fluid. The amount of fluid present in the body varies considerably at different times, the actual amount perhaps depending to some extent on the quantity of sodium chloride available. If the body happens to be low in fluids the ingested salt is retained in order that the fluid may be increased, for, as already indicated, the organism requires that every 100 c.c. of retained water should contain about 0.6 per cent. of sodium chloride. Under certain circumstances salt given to a healthy subject may be eliminated to a great extent, or retained in order to increase the total amount of body fluid.

To ascertain whether or not a patient excretes salt normally, it is necessary to get salt equilibrium established by careful dietary and to follow this with large doses of salt repeated for several days. If the salt is retained an increase in weight takes place both in the healthy and diseased individual owing to the increase in fluid, but since this increase, when it takes place in the healthy subject, is limited to a few days, the former passes out in his urine in the course of three or four days an equivalent amount of salt to that taken by mouth.

On the other hand, the nephritic whose salt elimination is deficient does not respond in this way, but accumulates more and more fluid until, if the ingestion of salt is prolonged, marked oedema and ascites intervene. Since it is difficult, under ordinary conditions, to investigate the salt retention on the above lines, it is necessary to rely for information on the estimation of chlorides in the urine passed on an ordinary diet.

For the estimation of urinary chlorides Volhard's method is very satisfactory, while for the blood and ascitic fluid we have used the plan suggested by MacLean and Van Slyke (9).

II. *The Effect of War Nephritis on Kidney Function.*

During the early stages of an acute attack of nephritis there appears to be more or less interference with the renal activity in general. Thus, in a severe case there may be marked retention of nitrogenous products in the

body with the usual abnormal ingredients in the urine: oedema more or less distinct is usually present, and the chloride content of the urine may be much diminished. Sometimes the diastatic value is very low, while in other cases it may be normal. After the first few days the condition is often succeeded by a copious diuresis by which the retained products are eliminated. In favourable cases this phenomenon is associated with a marked reduction or disappearance of oedema, and gradually the patient becomes convalescent; in course of time, varying from a few weeks to a month or two, the protein disappears from the urine and the renal function seems to be completely restored.

In other cases, however, there may be some early diuresis, but the patient does not progress very rapidly and feels unwell; on examination it is found that the blood still contains excess of urea, a condition which may persist for several months after the onset of the trouble. Such patients are often quite free from oedema and may pass only a comparatively small amount of protein in the urine, but the high blood urea figure persists, sometimes slowly decreasing and in other instances actually increasing. In such cases we have found that the diastatic reaction is of low value, and remains low for a considerable time after the blood urea has returned to normal. In some patients, on the other hand, there is no increase whatever in blood urea, and the diastatic reaction is found to be high, but the case is characterized by a persistent oedema and perhaps ascites.

From numerous investigations on cases of war nephritis which have been followed from a very early stage of the disease, it is quite certain that there are two very distinct types of the malady which can often be differentiated with certainty after the initial acute condition has passed over. As already indicated, all the kidney functions seem to be more or less in abeyance at this early stage, but this condition soon passes over, with the result that uneventful recovery may take place or a more or less tedious convalescence ensue. In the latter instance it is generally possible to divide the cases into two distinct groups in which the various tests give very different results.

In the first of these types the predominant feature is the tendency to retention of nitrogenous products (urea, &c.) in the blood. In this class of case the cardiovascular system often shows signs of degeneration: the urea concentration in the urine is decreased, and the diastatic reaction gives a low result. There is no oedema, and the urinary protein may be only moderate or slight in amount. For purposes of reference we may call this the *azotaemic* type.

In the second type the condition is markedly different. Oedema is present, and there is a tendency for the retention of chlorides. There is no retention of nitrogenous products, the diastatic reaction is high, and there is little or no cardiovascular involvement. A marked feature of this type is the large amount of protein generally present in the urine. Since its chief clinical manifestation appears to be a retention of water, and there is usually an excessive proportion of water in the blood, we will refer to this form as the *hydraemic* type.

These two types correspond in chemical findings and symptoms to the interstitial and parenchymatous forms of chronic disease, and it is interesting to

note that one or other of these types may be predominant even in acute nephritis where there is no suspicion of associated chronic disease.

There can be no doubt that the production of phenomena so entirely different in these two types indicates lesions in different parts of the renal system. Much has been written on the histological appearances of the kidneys in the different forms of chronic disease, but, unfortunately, the clinical findings so far have often not been easy to correlate with the histological changes found post mortem. Too much attention has been paid in the past to gross macroscopic appearances in the kidney. After all, it matters little whether a kidney is found to be large or small, white or red, rough or smooth, soft or hard. What is really of importance is to ascertain to what extent the kidney functions are interfered with during life, and it appears to us that little is to be gained by a more or less artificial grouping based chiefly on the naked-eye appearances of the organ after death. On the other hand, a careful attempt to correlate histological appearances with the clinical condition as indicated by chemical tests would probably give fruitful results.

Naturally we have had no opportunity of examining the kidneys of our cases for histological changes and so can furnish no direct observations on the matter, but for various reasons it appears probable that the azotaemic type is chiefly dependent on some lesion connected with the capillaries of Bowman's capsule and probably with other capillaries of the kidney, while the hydraemic variety appears to be associated with a lesion of the renal epithelium. In the first variety the essential lesion appears to be connected with the circulatory system of the kidney, while in the second the kidney cells are at fault.

In the acute case, if at all severe, manifestations of both the azotaemic and hydraemic varieties are present, since the kidney is probably suffering from a general invasion of the inflammatory process. As Auld (10) well expressed it, the kidney at this stage may be compared with a pneumonic lung. After the initial acute process has subsided the condition may entirely clear up, or convalescence may be associated with either the azotaemic or hydraemic type of symptoms or with a mixture of both.

Expressed in diagrammatic form this might be represented as follows :

Though these manifestations may be present, and yet apparently complete recovery ultimately take place, there can be little doubt that if they persist they give rise in course of time to the conditions represented by chronic interstitial and

chronic parenchymatous nephritis respectively. Of course, we are not quite certain that our apparently cured patients may not still be suffering from some defect which may reveal itself within the next few years, but so far as can be judged at present, several of these cases appear to have recovered. It is hoped that opportunities will arise in the near future to enable us to follow such cases for a number of years, so as to get information on several difficult problems of this nature. The important point, however, is that indications of the particular type of chronic disease which may ultimately develop in the event of an acute attack of nephritis failing to clear up, can be ascertained at a comparatively early stage, and while the patient is still suffering from the acute process. In fact, the nature of the subsequent development of the disease appears to be determined by the nature of the acute process, for the condition of the kidney that ultimately results in typical parenchymatous nephritis is, at an early stage of the acute process, certainly different from that which ends in chronic interstitial nephritis.

The following are the most marked differences, given in tabular form, between the hydraemic and azotaemic varieties of subacute nephritis. No doubt, in several instances, both conditions are present to some extent: in such cases one or other variety of the disease may predominate. Often, however, there seems to be a very hard and fast line between the two forms, so that a patient may show all the symptoms of the one variety without any of the conditions associated with the other type being evident.

<i>Azotaemic Form.</i>		<i>Hydraemic Form.</i>	
	(1) Oedema absent.		(1) Oedema present.
Urine.	(2) Protein present in urine, but often slight or moderate in amount.	Urine.	(2) Protein present in urine, often in very large amount.
	(3) Haematuria frequent.		(3) Haematuria absent.
	(4) Epithelial and granular casts often predominate.		(4) Small hyaline casts often predominate.
	(5) Chlorides present in normal amount.		(5) Chlorides diminished or may be absent.
	(6) Urea concentration decreased.		(6) Urea concentration normal.
	(7) Diastatic reaction low.		(7) Diastatic reaction normal or nearly so.
Blood.	(8) Tendency to increased amount of urea and other nitrogenous products in the blood.	Blood.	(8) No retention of nitrogenous products in blood.
	(9) Protein concentration often normal.		(9) Protein concentration tends to be low.
C. V. System.	(10) Heart enlarged and often tendency to arteriosclerosis.	C. V. System.	(10) Nothing marked.

The most obvious clinical difference between the two types of cases is the oedema and marked albuminuria in the hydraemic type, while the azotaemic

type shows no oedema, but is often associated with cardiovascular changes. Sometimes, as in the first case quoted below, the symptoms are more or less anomalous and cannot be brought into line with either of the two types described. This probably arises from the diffuse nature of the lesion. In the majority of cases, indications of one or other type are present, though combinations of both are not uncommon.

The following notes of cases indicate the chief chemical and clinical findings in the different types :

Case I (Fatal Case). Pte. M., aged 30. No previous illness. Onset 1.9.18 with general malaise and headaches. Oedema first noticed 11.9.18, and followed by vomiting and diarrhoea. Admitted with slight oedema of thighs and lumbosacral region and moderate ascites. He was at this time somewhat drowsy, and occasional facial twitchings were noticed. No thickening of radial vessel. Blood-pressure (systolic) 131 mm. Hg. Apex beat in left nipple line. Urine smoky, with much albumin. Occasional hyaline casts with numerous leucocytes, epithelial cells, and red blood corpuscles. The course of the case was steadily downhill, with repeated epistaxis, a subnormal temperature, vomiting, and diarrhoea. He died on 2.11.18.

In the following table the amount of urine and its urea concentration for the hour during which the blood sample was taken is given along with the blood urea and diastatic index of the urine.

Date.	Blood Urea in mg. per 100 c.c.	Urine Urea %.	Amount of Urine in c.c.	Diastatic Index.
17.9.18	249	—	—	—
25.9.18	331	0.91	31	2.8
1.10.18	380	0.99	20	2.8
5.10.18	461	1.14	35	4
11.10.18	530	1.11	47	3.3
21.10.18	592	1.20	75	10

A very marked inability to concentrate urea was obviously present, the urinary concentration being only two or three times that of the corresponding blood sample, while the figure for the normal individual usually amounts to more than fifty times the blood urea value. In the later stages the daily excretion of urine rose considerably, possibly owing to the diuretic action of the high blood urea, and at times as much as 2,000 c.c., containing 20 grm. of urea, were passed per day. At the time of his death the patient was free from oedema. In spite of the steady deterioration of his condition, the urinary diastatic index rose considerably, probably as the result of a rise in the diastatic index of the plasma from 10 to 28.

Cases of Azotaemic Type showing Prolonged Nitrogenous Retention in the Blood with or without a return to Normal Limits.

Case II. Pte. K., aged 45. Onset 4.8.18 with oedema preceded by shortness of breath and orthopnoea. Admitted to Field Ambulance 6.8.18. Total duration of oedema fourteen days. On admission to hospital no oedema. Radial slightly thickened. Apex beat internal to left nipple line. Urine smoky. Albumin marked. Fair numbers of epithelial and some hyaline casts. Macroscopic blood present until 21.11.18. On discharge apex beat in nipple line. Blood-pressure $\frac{182}{96}$. Radial vessel definitely thickened. Occasional headaches. Urine contained a faint trace of albumin and an occasional granular cast with a few red blood cells.

Some of the findings in this case are given in the table.

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentra- tion after 15 grm. Urea.	Amount of Urine in c.c. passed during 2 hours of Urea Test.
23.9.18	51	3.3	—	—
3.10.18	73	2	—	—
25.10.18	60	2	—	—
21.11.18	52	1.5	1.09	187
13.12.18	56	less than 1	0.99	226
23.1.19	43	1.2	1.21	241

Case III. Pte. B., aged 33. Onset 14.8.18, with shortness of breath followed by oedema and headaches. Oedema lasted only five days.

On admission to hospital, no oedema. Radial slightly thickened. Apex beat in left nipple line. Systolic blood-pressure 118 mm. Hg. Urine smoky. Much albumin with numerous casts, mainly hyaline and hyalo-granular with some epithelial. Macroscopic blood present in urine until 23.12.18.

On discharge radial was slightly thickened. Apex beat in the nipple line. Blood-pressure $1\frac{2}{4}$. Nocturnal frequency of micturition. Urine clear. Albumin faint trace. A few hyaline and epithelial casts present.

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentration Test.
23.9.18	65	less than 1	—
2.10.18	109	" 1	—
17.10.18	101	" 1	—
4.11.18	94	" 1	—
19.11.18	58	" 1	1.27 % (234 c.c. urine)
7.12.18	47	" 1	1.30 % (267 c.c. urine)
23.1.19	36	2	1.37 % (217 c.c. urine)

Case IV. Pte. S., 35 years of age. Shortness of breath noticed on 26.7.18. On 4.8.18, oedema with headache and vomiting. Admitted to Field Ambulance 8.8.18. Oedema disappeared on 10.8.18.

On admission to hospital there was no definite radial thickening. Apex beat external to left nipple line. Systolic blood-pressure 134 mm. Hg. Urine smoky, with a moderate amount of albumin and fair numbers of epithelial and some hyaline casts. Occasional headaches. Macroscopic blood persisted in the urine until 26.11.18. Apex beat on discharge (6.2.19) was one-quarter of an inch external to the left nipple line with a rumbling first sound at the apex. Blood-pressure $1\frac{4}{10}$ mm. Hg. Radial definitely thickened. Urine contained a faint trace of protein with some granular and hyaline casts. Polyuria was present.

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentration Test.
13.9.18	31	3.2	—
3.10.18	67	2.2	—
25.10.18	96	less than 1	—
14.11.18	74	" 1	1.13 % (379 c.c. urine)
4.12.18	62	" 1	—
20.12.18	46	" 1	1.12 % (191 c.c. urine)
24.1.19	37	" 1	1.19 % (623 c.c. urine)

Case V. Cpl. H., aged 28. Onset 1.9.18 with shortness of breath, followed by oedema and headache. Immediately before admission to hospital he had two severe malarial rigors. On admission he was very anaemic, with slight oedema of the ankles and slightly thickened radial. Apex beat in left nipple line. Systolic

blood-pressure 99 mm. Hg. Spleen palpable. Urine deeply smoky, with moderate amount of albumin and numerous granular casts and some red-blood cells.

Oedema cleared on 30.9.18. Macroscopic blood in the urine until 18.11.18.

On discharge (1.2.19) the apex beat was internal to the nipple line. Blood-pressure $\frac{120}{73}$. Urine was free from albumin, and only a few hyaline casts were seen.

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentration Test.
25.9.18	209	less than 1	—
1.10.18	71	1	—
8.10.18	37	3.3	—
21.10.18	47	5	—
8.11.18	41	1.4	1.55 % (258 c.c. urine)
6.12.18	29	2	1.55 % (236 c.c. urine)
27.1.19	31	10	2.02 % (222 c.c. urine)
30.1.19	—	6.6	—

In these last four cases the blood urea slowly returned to a concentration approximating the normal. This diminution in the blood urea concentration was accompanied by an increase in the daily urinary measure, but the urea concentration in numerous samples tested remained low. In Cases III and IV, the fall of urea in the blood was probably quickened by an increase in fluid ingestion—these two patients receiving about 3,000 c.c. fluid daily for a considerable period. In the first three cases of the azotaemic type it will be noticed that though the blood urea fell, the concentration with the urea test remained low, and there was no marked rise in the diastatic index. In these patients evidence of arterial changes was present on discharge, and in two of them cardiac hypertrophy and a raised blood-pressure were also found. The disappearance of nitrogenous retention probably indicated the attainment of compensation, but by no means a complete recovery of kidney efficiency.

In Case V evidence of improvement accompanied the fall of blood urea as indicated by a rising diastatic and an increased capacity for concentrating urea. This is a good example of a case in which recovery, though very delayed, ultimately takes place.

Cases of the Hydraemic Type.

Case VI. Pte. R., aged 41. Onset with headaches on 14.8.18, followed by oliguria, and on 14.9.18 by oedema.

Admitted to hospital on 4.10.18 with oedema of back and ankles. Radial vessels not thickened. Apex beat just internal to left nipple line. Blood-pressure $\frac{100}{68}$ mm. Hg. No macroscopic blood in urine. Albumin very pronounced, and considerable numbers of hyaline and hyalo-granular casts with a few epithelials present. The oedema was still present on discharge on 7.2.19, and at times ascites could be demonstrated. The urinary condition remained unchanged and no cardiovascular changes were noticed. Blood-pressure on discharge $\frac{120}{82}$.

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentration Test.
4.10.18	36	6.6	—
17.10.18	29	10	—
13.11.18	24	10	2.38 % (100 c.c. urine)
2.12.18	—	1.6	—
3.12.18	57	5	1.07 % (163 c.c. urine)
10.12.18	38	6.6	1.82 % (237 c.c. urine)
16.1.19	26	10	—

In this patient the blood urea concentration was within normal limits, except on 3.12.18, when it rose to 57 mg. apparently as the result of some condition which caused the appearance of a patch of consolidation in the left lung with an initial rigor followed by three days' pyrexia. At the same time, as indicated in the above table, there was a marked fall in the diastatic and a lowered concentration with the urea test. The appearance of the increased urea percentage in the blood was followed by a transitory diuresis, as much as 3,600 c.c. of urine being passed in one day. This, however, ceased with the return of the blood urea to normal limits, and was not sufficiently prolonged to clear the patient entirely of oedema. A high degree of albuminuria persisted throughout the patient's stay in hospital, but no blood was ever found in the urine. Cardiovascular changes were absent, and the diastatic index remained high.

In a similar type of case with persistent oedema, ascites, and marked albuminuria, but no cardiovascular changes, the following were the findings:

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentration Test.
30.8.18	34	10	—
15.9.18	27	6.6	2.37 % (146 c.c. urine)

In both the above cases the urinary chlorides were much diminished.

The following two cases may be regarded as instances of the mixed type:

Mixed Type of Case with Azotaemic and Hydraemic Symptoms.

Case VII. Pte. G., aged 48. Onset on 1.7.18 with oedema and shortness of breath. Admitted to Field Ambulance 14.9.18, and to this hospital on 24.9.18. On admission there was considerable oedema of the back, thighs, and ankles, with basal pulmonary oedema and ascites. Radial artery moderately thickened. Apex beat just external to the left nipple line. Blood-pressure $1\frac{5}{8}$. The urine contained much albumin and fair numbers of hyaline, hyalo-granular, and epithelial casts. The oedema steadily persisted until 18.11.18, when it finally cleared up on drastically reducing the patient's salt ration. From 14.10.18 to 23.10.18 macroscopic blood was present in the urine. Slight oedema recurred at the end of December. On discharge the blood-pressure was $1\frac{4}{8}$, the urine containing considerable amounts of albumin and fair numbers of hyaline and granular casts, with an occasional epithelial cast.

The course of this case is indicated in the following table.:

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentration Test.
25.9.18	264	6.6	—
1.10.18	151	6.6	—
8.10.18	118	10	—
14.10.18	62	10	—
21.10.18	57	6.6	—
4.11.18	70	10	—
19.11.18	48	4	—
10.12.18	38	1.5	1.46 % (235 c.c. urine)
21.1.19	52	2.2	1.37 % (184 c.c. urine)
21.1.19	—	4	1.41 % (252 c.c. urine)

Case VIII. Pte. M., aged 41. Oedema, headache, and shortness of breath developed on 12.8.18. He was admitted to this hospital on 25.8.18 with moderate oedema of back and ankles. Radial slightly thickened. Apex beat internal to left nipple line. Systolic blood-pressure 145 mm. Hg. Urine contained much

albumin and numerous hyaline, hyalo-granular, and epithelial casts. Oedema persisted until 29.10.18, and disappeared after markedly reducing his salt ration. From 12.10.18 to 29.10.18 the urine was smoky. He was discharged on 1.2.19 with evidence of slight cardiac hypertrophy, slight radial thickening, and a blood-pressure of 145 mm. Hg. The urine was then free from blood, but showed a very considerable amount of albumin and some hyaline epithelial casts.

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentration Test.
31.8.18	56	3.3	—
2.10.18	37	4	—
14.10.18	33	4	—
13.11.18	28	4	1.43 % (180 c.c. urine)
16.12.18	34	2.5	1.33 % (153 c.c. urine)
16.1.19	34	2.3	1.85 % (158 c.c. urine)

In both these cases there was initial urea retention, in one case prolonged with a falling diastatic index. The concentration with the urea test was on the low side, and cardiovascular changes with occasional haematuria were present. At the same time the ability to excrete chlorides was impaired and the prolonged oedema only cleared on strictly limiting the ingestion of salt. Persistent oedema and marked albuminuria which does not tend to clear up readily differentiates these cases from the pure azotaemic type.

A few instances may be given of milder cases in which there was not apparently at any time any severe defect in the excretory function of the kidney while under our observation, and in which on discharge renal efficiency seemed to be good.

Examples of Milder Cases in which Kidneys seemed efficient.

Case IX. Pte. B., aged 42. Onset with oedema of six days' duration on 28.8.18. Slightly thickened radial. Apex beat in left nipple line with a blowing systolic murmur. Blood-pressure 118 mm. Hg. Urine contained a moderate amount of albumin with numerous hyaline and hyalo-granular casts. Discharged 29.1.19 with a faint trace of albumin and a few hyaline casts. Blood-pressure $121 \frac{1}{71}$.

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentration Test.
19.9.18	28	4	—
17.10.18	32	5	—
13.11.18	30	6.6	2.14 % (147 c.c. urine)
27.1.19	37	6.6	2.37 % (135 c.c. urine)

Case X. Pte. D., aged 26. Onset with headache, shivering, and probably haematuria on 14.7.18. On admission to this hospital no oedema or cardiovascular changes. Urine contained a small amount of albumin with some epithelial and hyaline casts. No macroscopic blood. On discharge on 26.1.19 no cardiovascular changes. Blood-pressure $128 \frac{2}{80}$. Urine contained a trace of albumin with a few hyaline casts and an occasional epithelial cast.

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentration Test.
16.9.18	41	10	—
28.10.18	28	4	—
25.11.18	34	5	2.07 % (132 c.c. urine)
12.12.18	32	5	2.20 % (136 c.c. urine)
24.1.19	32	6.6	2.79 % (130 c.c. urine)

Case XI. Pte. M., aged 20. Onset 19.8.18 with oedema which lasted three days only. On admission to hospital no definite cardiovascular changes. Blood-pressure 102 mm. Hg. Urine was smoky, with a small amount of albumin and a fair number of epithelial and small granular casts. Haematuria lasted for three days after admission. On discharge on 20.12.18 the urine was free from albumin and casts.

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentration Test.
10.9.18	20	10	—
5.10.18	36	6.6	—
15.11.18	24	5	2.67 % (127 c.c. urine)
18.12.18	23	10	2.74 % (124 c.c. urine)

Case XII. Pte. L., aged 34. Onset with shortness of breath on 18.7.18. Oedema 1.8.18, with vomiting, headache, and oliguria. Admitted to Field Ambulance on 8.8.18. Oedema subsided in three days. On admission to hospital, cardiovascular system appeared to be normal. The urine contained a trace of albumin and a few hyaline casts.

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentration Test.
10.9.18	20	10	—
4.10.18	24	10	—
12.11.18	27	10	2.07 % (121 c.c. urine)
12.12.18	—	10	2.42 % (140 c.c. urine)

In these cases the attack seems to have left little, if any, impairment of renal function. No increase of blood urea was observed, the oedema was of short duration, cardiovascular changes were absent, the diastatic index approximated the normal, and haematuria, if present, was of short duration. The ultimate chemical findings were also satisfactory.

III. *Observations on Treatment.*

The active treatment of acute nephritis reduces itself largely to the treatment of symptoms, and with this we are not concerned here. The principle, however, is generally accepted that a low protein diet is indicated in the early stages, especially in cases in which there is a retention of nitrogenous products. Very often this low protein diet is regulated according to the amount of protein appearing in the urine, so that in certain cases it is the practice of medical men to persist with it for long periods. Often milk is made use of in this connexion, and it is not infrequently forgotten that milk is a form of food comparatively rich in proteins. On general principles it is probably correct treatment to give low diets, especially as regards protein, during the early stages of the malady; but it is by no means certain that protein does any harm, especially during the subacute and convalescent periods of the disease. Though it is often enough inferred in the literature that an increase in protein intake tends to raise the total percentage of protein in the urine, we have obtained little evidence of this in our cases. In the urines of several patients examined by us, little or no increase in the urinary

protein could be ascertained after protein meals, and we are inclined to think that if this alleged increase in albuminuria after ingestion of protein takes place at all, it is a much rarer phenomenon than is generally supposed.

On physiological grounds it is difficult to understand why protein, which according to modern teaching is hydrolysed in the intestine and resynthesized by the tissues from the amino-acids in the blood, should increase the protein of the urine. No doubt, it is a difficult question to decide whether or not a large protein meal immediately increases the blood protein, but if it does so at all it can only do it to a very slight extent if we accept as correct the modern ideas on protein metabolism. Indeed, so far as the evidence goes, it would appear that blood protein is only slowly built up, just as is the case in other tissues. The point to be noted is that protein is essentially different from such a substance as sugar which is absorbed as such into the circulation, and tends to increase directly the blood sugar concentration.

Further, there is no evidence that protein causes any injurious effects in the type of renal disease in which there is no tendency to nitrogenous retention—the hydraemic type. Indeed, we really do not know whether protein in ordinary amount does harm even in azotaemic cases where there is a tendency to nitrogenous retention, but in the present state of our knowledge it seems wise, on general principles, to enforce certain restrictions as regards protein in such patients. It must, however, be borne in mind that patients suffering from subacute nephritis should have a sufficient amount of food, for the detrimental effect of an insufficient diet retards progress. In the two different types of nephritis, however, modifications in the dietetic treatment are indicated. With regard to water it was our custom to give unlimited amounts to the azotaemic type of patients during the subacute stage, and even to encourage drinking. In the hydraemic variety the intake of fluids was naturally kept moderately low.

Diet in the azotaemic type. In the azotaemic type of nephritis we have proceeded on the principle that a low diet is indicated during the acute stage, and that this should be followed, at least for some time, by a diet of reduced protein content but rich in carbohydrates and fats. Sometimes such a diet may give rise to digestive disturbances, but this is rare. After a month or two, depending on the severity of the case, all our patients were put on ordinary hospital diet.

Diet in hydraemic type. In the hydraemic case, after the acute stage is over, the conditions are entirely different. Here there is no tendency to retain nitrogen, and no apparent reason exists why protein should not be given in the usual amount. Since this type of case corresponds to the chronic parenchymatous variety, we have adopted in our hydraemic cases the method of dietetic treatment recommended by Epstein (11) in parenchymatous nephritis. In this condition, in which one of the most trying symptoms is pronounced oedema often accompanied by ascites, Epstein found that feeding with a diet of very high protein content often resulted in a decrease or removal of the dropsy. This beneficial result he ascribed to an increase in the protein of the blood plasma.

In these cases there is generally a large amount of protein lost in the urine, and Epstein concluded that this drain of protein resulted in a low protein concentration in the blood, which lowered the plasma osmotic pressure to such an extent that water escaped from the blood-vessels into the tissues. The increased protein diet, by raising the plasma protein content, augmented the power of the plasma to retain water in the blood-vessels and so prevented an accumulation in the tissues. The water retained in the blood was of course thrown off by the kidneys instead of being passed on to the tissues.

That a high protein diet often results in removal of the dropsy in chronic parenchymatous nephritis is certain, but the cause of this is not very easy to ascertain with certainty. While increase of plasma protein may be a factor in some cases, it is certainly not the essential one, for we have seen a case, in which the oedema and ascites were exceedingly severe, clear up in two months without any increase of the protein in the blood. Particulars of this case are given below (Table III). Here it will be seen that the blood protein remained practically constant; indeed, if anything, it showed a slight tendency to decrease. This patient suffered from ascites so pronounced as to necessitate tapping every two weeks. At each tapping from 8 to 12 pints of fluid were removed; oedema was also extreme, and for over six months the patient had been bedridden.

The urine contained only the faintest trace of chlorides.

On October 14, 1918, he was put on the high protein diet recommended by Epstein. For some little time his condition remained unchanged, but gradually during the next three months his daily output of urine rose from an average of 20 to 25 ounces to a maximum of 80 to 100 ounces. He was tapped on November 15 and on December 6, when 12 and 10 pints of fluid respectively were removed. Since his last tapping, now over six months ago, he has been free from ascites and oedema, has put on flesh, and looks and feels much better. The renal condition is, of course, not cured, for he still continues to pass large amounts of albumin (from 12 to 20 gm. per day), but his general physical comfort is increased to such an extent that life, which was formerly so trying for him, is now comparatively pleasant. On his present diet he is passing from 2 to 3 gm. of chlorides per day.

A case very similar to the above has recently been described by Clifford Allbutt (12).

TABLE III.

Details of Blood Protein and Urea in above Case.

Date.	Protein in Plasma.	Urea in Blood.
October 13, 1918	6.29 %	27 mg. per 100 c.c.
November 20, 1918	6.20 %	64 "
December 3, 1918	6.00 %	56 "
January 3, 1919	—	81 "
January 22, 1919	5.96 %	63 "

The effect of urea in causing diuresis in nephritis. Since the protein content of the plasma of this patient tended rather to decrease than increase, it is certain

that, in this instance at any rate, Epstein's explanation does not hold. What then could have been the cause of the marked diuresis by which the waterlogged cavities and tissues were drained? We are inclined to think that the explanation lies in the increase of blood urea consequent on the enhanced protein diet. Urea acts normally as a powerful diuretic in cases where there is available fluid for excretion, and has been credited with results in parenchymatous nephritis where other diuretics have failed to act (13). From an initial value of 27 mg. per 100 c.c. of blood the urea rose to a maximum of 81 mg., being generally in the neighbourhood of 60 mg. Now this amount of urea should be sufficient to stimulate marked diuresis, and in order to test this we tried the effect on a similar case of continuous doses of urea given by mouth. Here, again, the quantity of urine was more than doubled, though other diuretics had little effect. Unfortunately, this patient refused to continue taking the urea owing to its unpleasant taste and its tendency to cause sickness; it was obvious, however, that the treatment had resulted in a reduction of the dropsy.

In still another patient suffering from the hydraemic variety of war nephritis with persistent oedema, a slight pulmonary complication ensued accompanied by a temporary urea retention in the blood. Here the urea rose from 24 mg. to 57 mg. Three days afterwards a copious diuresis occurred, and continued until the blood urea content reached normal, the result being that the original troublesome oedema was much decreased.

This effect of urea probably explains the cause of the marked diuresis so often seen in acute nephritis after the first few days. In these cases there is a tendency for the retention of the urea, water, and other ingredients. The urea content of the blood increases and the tissues contain an excess of water. Soon the kidney recovers somewhat from the original inflammatory invasion and the renal cells begin to functionate more normally. Here, then, we have all the conditions making for a profound diuresis—an increased blood urea content, excess of water in the tissues, and a recovering kidney.

The consequence is that in ordinary cases diuresis goes on until the oedema disappears, or until the blood urea returns to its normal level. Indeed, it would seem as if the storing up of urea acts as a provision of Nature to ensure the rapid removal of retained fluid.

In chronic parenchymatous nephritis there is no tendency to retain urea while the patient is on ordinary protein diet, but on a much increased diet, such as that recommended by Epstein, the blood urea concentration is appreciably increased, with the result that diuresis follows. Whether or not this is the full explanation of the phenomenon, there is little doubt that it plays an important part.

If we accept the teaching that a large amount of protein food is indicated in parenchymatous nephritis with dropsy, we are confronted with the apparently anomalous principle that in cases where there is much albuminuria (nearly always parenchymatous cases) the larger should be the amount of protein given in the food. This is, however, quite reasonable on various grounds, since the

actual daily loss of protein by the urine is very appreciable and some attempt should be made to compensate the body for this loss. Also, if the increase in blood urea is the chief or only factor in the causation of diuresis, it is much more pleasant to induce the condition by means of protein food than by the more direct but unpleasant method of giving urea by mouth.

The withholding of salt is also of much value in certain mild hydraemic cases, for in several of our patients oedema persisted as long as the ordinary amount of salt was permitted in the diet, but rapidly subsided on cutting off salt. In cases of severe parenchymatous dropsy, however, a so-called salt-free diet often fails to have any appreciable effect.

IV. *Discussion of Tests for indicating Kidney Efficiency.*

The question of the efficiency of the kidney in patients with subacute and chronic nephritis is of great importance, especially at the present time, when so many men are suffering from the effects of war nephritis. That the presence of albuminuria does not afford much help is obvious, when we consider that over 5 per cent. of the apparently fit men on active service had some albumin in their urine and that 2 per cent. of these had gross albuminuria (14). Further, the extent of the albuminuria is of little value as an index to the gravity of the case, for it is well known that the more serious cases may show but traces of albuminuria. In general, the amount of protein in the urine in subacute and chronic cases is probably of more importance in indicating the predominating type of disease present than in furnishing information as to the gravity of the renal condition.

In the early stages of an acute attack of nephritis the blood urea content furnishes the best indication of the state of the kidney. If, this is normal, it may, be taken for granted that the damage to the kidney is not sufficient to interfere with its normal function of excreting nitrogenous products. If, on the other hand, the blood urea figure is high, the most valuable information as to the progress of the disease is obtained by occasional estimations of blood urea. If the urea tends to get less, the prognosis is good; if it gets persistently higher, the outlook is correspondingly bad. In severe chronic interstitial conditions the same state of affairs is present.

In many subacute and chronic conditions the kidney is not sufficiently damaged to cause an increase in blood urea, and so no information is to be obtained by this test. In such cases other means must be employed, and we have found that the capacity of the kidneys to concentrate urea in the urine, under the conditions already fully described, affords very helpful information. If, after receiving 15 grm. of urea by mouth, the patient excretes urine containing 2 per cent. or so of urea, it is safe to conclude that the kidney is at least fairly efficient. If the urine concentration is low, it is in the great majority of cases an indication that the kidney is inefficient. As already mentioned, it sometimes happens that the normal diuresis caused by urea tends to give a urine of low urea concentration in a healthy subject, but this difficulty can be overcome by

discarding the specimens of urine passed during the first two or three hours after the administration of the urea and examining a later specimen. In conjunction with the above test the estimation of the diastatic index is of great value. Usually the indications given by both tests agree, and when one goes down the other also decreases, and vice versa. In cases where functional tests such as the above indicate that the renal function is being efficiently carried out, it is important to investigate the condition of the cardiovascular system, for the indirect danger of cerebral haemorrhage or cardiac failure may be much greater than any direct manifestation arising from kidney inefficiency.

Besides the above methods we have used several other tests from time to time. Of the various dyes used in this connexion the most popular at the present time is phenolsulphonephthalein. This dye seems to give a very good indication of the state of the kidney function in general, but, in our experience, fails to differentiate between the different types of nephritis. When the kidneys are capable of secreting from 40 to 50 per cent. of the dye in one hour, there is probably not much disturbance of function, but it appears to us that the test is not sufficient by itself to give the required information in the absence of other methods of investigation. In conjunction with other tests it is undoubtedly of much value.

Finally it is most important to emphasize that, whatever the result of the various functional tests may be, no prognosis should be given without first carefully examining the state of the cardiovascular system.

REFERENCES.

1. MacLean, F. C., *Journ. Exper. Med.* 1917, xxvi. 181.
2. Hewlett, Gilbert, and Wickett, *Archiv Int. Med.*, Chicago, 1916, xviii. 636.
3. Van Slyke and Cullen, *Journ. Biol. Chem.*, Baltimore, 1914, xix. 219.
4. Wohlgemuth, *Biochem. Zeit.*, Berlin, 1908, ix. 1, and 1909, xxi. 381.
5. Corbett, *Quart. Journ. Med.*, Oxford, 1912-13, vi. 351.
6. De Wesselow and MacLean, H., *Reports of the Committee on War Nephritis*, No. 3, II, June 1918.
7. MacAllum, A. B., *Trans. Coll. Physicians*, Philadelphia, 1917, xxxix. 7.
8. Vallery-Radot, *Études sur le Fonctionnement rénal dans les Néphrites chroniques*.
9. MacLean, F. C., and Van Slyke, *Journ. Biol. Chem.*, Baltimore, 1915, xxi. 361.
10. Auld, *Brit. Med. Journ.*, 1917, ii. 414.
11. Epstein, *Amer. Journ. Med.*, 1917, N.S., cliv. 638.
12. Clifford Allbutt, *Brit. Med. Journ.*, 1918, ii. 395.
13. Cushny, *The Secretion of the Urine*, Lond., 1917.
14. MacLean, H., *Brit. Med. Journ.*, 1919, i. 94.