CHRONIC NEPHRITIS, WITH A DISCUSSION OF FUNCTIONAL TESTS

CLINIC GIVEN AT THE BRIGHAM HOSPITAL, BOSTON, MASS.

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REPRINTED FROM INTERNATIONAL CLINICS, VOL. III, SERIES 27

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I BROUGHT over this morning two patients, as a text, to speak on some of the renal functional tests, as I do not think that I ever explained to you anything about them. The first patient here, the boy (No. 4693), is fifteen years of age, and his history can be summarized as follows:

For a year he has had headache, nausea, vomiting, and blurred vision, not continuously, but intermittently. He has had œdema of his legs and face. There is no history of any disturbance in micturition or any abnormality of the urine from inspection. Very recently he has developed a suppuration in one of his ears, and comes in with a discharging right ear. There is no evidence of mastoid tenderness. His heart is somewhat enlarged and forceful in action. His blood-pressure is somewhat elevated: when he came in the systolic pressure was 160 and the diastolic just a little over 90. Since he has been in the hospital it has fallen gradually to 140 systolic, with very little change in the diastolic, but for a boy of thirteen that increase is more hypertension than the figures would indicate in an adult. His eye-grounds show slight changes. The disks are obscured, there is definite œdema of the disk cup, and a little evidence of exudate in the adjacent retina. You notice that he gave the complaint of blurring. He had difficulty in seeing at school. He has some enlargement of the heart, which I have already mentioned. He has a trace of albumin in his urine and a variety of casts.

Now, the etiology of this case is uncertain—that is, as representing the starting point of the nephritis. The ear infection and symptoms of it are rather recent. The symptoms referable to his renal lesion are of a considerably greater duration, so probably there is no association between the ear infection and the nephritis, from the point

* Stenographic report of a clinic for the Third Year Class of the Harvard Medical School.

of view of cause, other than that the ear infection probably brought about some recent exacerbation of the renal involvement. The only infection that he has had was a pneumonia, which was eight years ago. Pneumonia at times, but not very commonly, starts a chronic renal involvement. The other acute infectious diseases commonly associated with nephritis have not occurred in this boy. Since he has been in the hospital he has had slight elevation of temperature, probably associated with his ear infection. He has had a rather small output of urine, but it has been proportionate to his intake of fluid—about an even balance. Of course, that represents, so far as he is concerned, you might say, a diuresis. The fluid referred to here, however, is that which is measured as fluid and taken into the body as such. Part of the time this boy was on a soft solid diet, and that contains a considerable amount of fluid which is not measured. Then he has been on a diet low in protein which carries a corresponding, but not quite so great, amount of liquid contained in food. It is to be remembered that in all these charts we do not make any attempt to measure the amount of fluid contained in food. For instance, carrots contain 85 per cent. water. The boiled or cooked carrot does not contain so much, but contains a very considerable amount. These patients all get a great deal more water than we tabulate here as fluid. What we tabulate are water drunk, milk, coffee, and actual liquid foods, and the normal relation is about two-thirds of the intake is excreted as urine, and the average patient, who puts out about 1000 or 1200 Cc. of urine, would be having an intake correspondingly above that. These percentage relations decrease as the fluid intake increases, so that where it would be two-thirds on the lower levels, on the higher levels it usually does not show such a great difference, but the average probably is about 800 to 1000 Cc. difference between the fluid intake and the urine output. We consider that approximately a normal figure.

Now, besides these indications of nephritis, this boy has a *phthalein output* of 24 per cent. in the first hour and 15 per cent. in the second hour, a total of 39 per cent., which, as you know, is a marked reduction of the phthalein output, the normal being from 60 to 75 or 80 per cent., and it is questionable whether figures as low as 50 per cent. ought to be regarded as normal, although some people excrete about 50 per cent. of the phthalein and give no other indications of a renal

lesion. The *blood urea nitrogen* in this boy is 21 mgm. per 100 Cc., the index of urea excretion is 75 per cent. His phthalein output is 39 per cent., his index of urea excretion is 57 per cent., both figures indicating a moderately decreased renal function. I will speak in a moment about the significance of the urea excretion when we get through with the other case. There is no œdema. The only signs in the boy now to be made out on examination are the hypertension, cardiac hypertrophy, and the slight changes in the eye-grounds.

This other patient (No. 4683) is twenty-four years of age. He gives the past history of palpitation of the heart, shortness of breath, and headache, covering a period of about four years. There is no disturbance in micturition, and no abnormality observed in the urine. Five days before he came into the hospital he had, in the morning when he woke up, a severe headache; the next day he noticed that his legs were swollen. His friends pointed out to him that his face was puffy, so that he has had recently, in addition to shortness of breath, palpitation, and headache, the added feature of œdema of his face and legs. His blood-pressure was 190 systolic and 120 diastolic when he came in. It has fallen to 160 systolic and 100 diastolic during the period that he has been in the hospital. His urine shows a trace of albumin and a few hyaline and cellular casts, a few leucocytes, and a few red cells. He had typhoid fever as a child; he had grippe two years ago. Apparently he has not had any of the other acute infectious diseases, but his command of English is not good enough to be certain about these negative statements. His grippe, you see, as in the boy, does not explain the beginning of the renal process, because the renal symptoms existed before he had grippe. Typhoid fever rarely produces a renal lesion. It does occasionally, but it is very unusual. It is not at all improbable, however, that that was not typhoid, but typhus, that he had as a child, in which case there is much more probability of having subsequent renal lesion, but it is not clear in his case just what infection started the renal lesion. He did not have tonsillitis, and apparently did not have scarlet fever, typhoid, or measles, all of which are fairly frequent causes of nephritis, but he had grippe, though not prior to the beginning of his symptoms. Just immediately before he came in he had an acute infectious abscess in the buttock, following trauma, which may have played a part in the recent œdema in the sense of an acute exacerba-

tion of a chronic renal lesion. His phthalein output is 60 per cent. and his index of urea excretion is 80 per cent., both within normal limits, so that his function of excretion of a dyestuff and his index of excretion for urea are not disturbed. His function for the excretion of water was disturbed, and he had œdema, but since he has been in the hospital he has been losing his œdema, having a diuresis averaging 1600 Cc., with an intake of fluid less than 1000. When he was first in the hospital he had a diet with a maximum of about 75 Gms. of proteid, containing on the average about 5 Gms. of salt (sodium chloride).

The Wassermann reactions were negative in these patients, and there is nothing else particularly important in the histories or in the physical examinations. They both represent types of chronic renal lesions in relatively young individuals, with an associated hypertension and coincident cardiac hypertrophy. There is no evidence of actual damage to the heart in either case from the point of view of myocardial insufficiency, so far as observation goes. So far as this patient is concerned, he has had some palpitation and dyspnœa, indicating that his heart has been working against increased pressure, and that has had no effect on the myocardium to lessen its function.

Both of these patients have about normal amounts of urea nitrogen. This patient with a normal index has 13 mgm. per 100 Cc., which is essentially normal. This boy with decreased index down to 57 per cent. has a moderately increased urea nitrogen in the blood, 21 mgm. per 100 Cc. In these two cases the index of excretion pretty well parallels the difference in the blood urea, the one with the high amount of blood urea having the lower index, and the one having the lower amount of blood urea having the high index. That, however, is not always true. The phthalein excretion you are quite familiar with, its significance and method of determination, etc. The *index of urea excretion* we owe to Doctor McLean, of the Rockefeller Hospital, in so far as the formulæ we are utilizing are concerned. The principle on which it is based we owe to Ambard, the French clinician, who pointed out that there were definite laws governing the excretion of urea, and that in normal individuals that could be reduced almost to a constant factor, and his formula was 0.08 as the average normal and varying from 0.075 up to 0.09. That means that if you have in the blood a certain amount of nitrogenous substances

in the form of urea, if that blood is circulating through the kidney at a normal rate, and if the kidney bears a normal ratio to the size of the individual, the rate of excretion of the urea in the urine will bear a constant relation to the amount of concentration of the urea in the blood. If there is more urea in the blood there will be more urea in the urine, and the reverse will be true. Furthermore, if you feed your patient a high proteid diet instead of a piling up of urea or other nitrogenous substances, you simply increase the excretion of these substances in the urine. If the kidney is damaged, instead of getting out into the urine the average amount in the average time, other factors being the same, you will have a piling up of the urea in the blood, but you may have a damaged kidney in which the urea in the blood is not piled up, either because ingestion and absorption of nitrogenous substances are decreased, or, more probably in this case, because the nitrogenous substances, instead of being in the blood ready to be excreted from the kidney, are displaced from the blood in the other direction and are taken up in other body channels and other tissues, so the amount of urea nitrogen in the blood does not bear a definite relation to normal conditions.

But there is a definite relation between the rate of excretion from the kidney and the amount in the blood which can be expressed in the form of a formula, and this is the formula which we are now using:

$$\text{Index} = \frac{\text{Gm. urea per 24°} \sqrt{\text{Gm. urea per litre of urine}} \times 8.96}{\text{Weight in kilos} \times (\text{Gm. urea per litre of blood})^2}$$

It is based on Ambard's figures. Ambard's formula gave for a normal individual a figure like that (0.08). In normal individuals the figure varies from that point up or down by relatively small amounts. By taking the fact that the rate of excretion from the urine bears a relation to the amount of urea in the blood, which is more or less constant for a normal individual, and by utilizing that constant of 0.08 in a formula we can convert that formula, by using 8.96 as the constant, into one that gives for a normal individual 100 per cent. and express departure from the normal in a percentage increase or decrease, and that is what the formula of McLean expresses.

Now, to get those figures, certain methods have to be followed.

In the first place, the rate of urea excretion is not obtained by determining the amount of urea in the 24-hour amount of urine, but is determined in a shorter period of time. We usually take one hour and forty minutes or two hours and collect the urine during that period of time, and in the midst of that period of time, if you take a two-hour period at the end of one hour, we take the blood from the patient and determine the urea content of the blood. Then we convert that into the rate of excretion in the urine, taking a two-hour period, by multiplying by 12, so that if an individual puts out a certain amount of fluid in the two hours containing a certain amount of urea we say that if he kept on excreting at that rate for the 24 hours he would have excreted so many cubic centimetres of urine or so many grammes of urea, rather than taking the actual amount in 24 hours, because we want to get the relation between what is in the blood and the rate of excretion in that period of time. If we shorten the period too much, we get down to a relatively small figure, with a greater possibility of error. If we lengthen the period beyond two hours, we begin to estimate urinary conditions fairly remote from the urea content in the blood taken half-way between.

The other thing you have to take into consideration is to make this test far enough from a meal so as to establish an equilibrium for the absorption of the urea and not interfere, in the middle of the test, by the ingestion of fluids or food. So we begin the test several hours after a meal and give the patient, prior to the test, a considerable amount of fluid so as to get a good flow of urine, and during the two-hour period the patient receives no food or fluid. So the rate of urea excretion is converted into the amount of urea excreted per 24 hours, measured in grammes; that is, that figure is in grammes. That is secured by multiplying the length of the period of observation by the necessary figure to convert the actual period of observation into 24 hours. The concentration in the urine is the amount of urea, expressed in grammes, that would be present in a litre of urine. Then the constant necessary to make this index of excretion in a normal individual, with a figure 0.08, equal to 100 per cent. is 8.96, so that this constant is replaced by the actual figure, 8.96. Then the weight of the patient is expressed in kilogrammes, and the urea content in the blood is the amount of urea per 1000 Cc. expressed in grammes. So we get this formula of McLean, as given above, and in practice

the calculation is made with a slide rule to save time and is done mechanically.

STUDENT: Where do you get 8.96?

That is the necessary figure for the constant in order to reduce it to 100 per cent. That is, if the formula is worked out, and in the place of all of those are supplied figures for normal individuals which all normals practically give, then the figure with Ambard's figures gives 0.08. If you substitute actually so that all formulæ are substituted by actual figures except the constant, and if you figure out in order for the answer here to be 100 per cent., the constant has to be 8.96. In a sense that is a perfectly arbitrary figure which is founded on the relationship in normal individuals. So there is nothing significant in it. It is just obtained from the preceding formula and substituted there.

Now I have put down some of McLean's figures * to indicate that with about the same amount of urea nitrogen in the blood you can get very considerable variations in your index of excretion. In other words, that index gives us subdivisions in severity of lesion which are not indicated by the actual amount of urea nitrogen accumulated in the blood, and also with normal figures for the urea in the blood you may get disturbances of very considerable degree, indicated by the index of excretion, so it is a more delicate barometer of changes in renal function than the simple estimation of the urea nitrogen. Those figures you see are expressed in grammes per litre. We have usually expressed ours in mgm. per 100 Cc. because we have gotten accustomed to doing it on account of that method having been followed in Doctor Folin's early work. Of course, 0.48 gramme per litre is 48 mgm. per 100 Cc. of blood. This one with 48 and this one with 48 show a very considerable difference in the other figures. This patient has an index of excretion of 91 per cent. and 58 per cent. phthalein. The index is just a little below the theoretical 100, but not enough below to call it abnormal, and the phthalein output is just a little below the normal phthalein output, whereas this patient with the same amount of urea nitrogen has a phthalein output of 25 per cent., a very considerable reduction, and an index of excretion down to 18 per cent., a reduction from 100 per cent. to 18 per cent. Here is another patient, 45 mgm. urea nitrogen per 100 Cc., index 44 per

* Ref. McLean, *Jour. A. M. A.*, 1916, lxvi, 415–421.

cent. and phthalein 33 per cent. This one has 37 mgm. urea nitrogen, index of 37 per cent., and 27 per cent. phthalein output, but in general the high figures for urea nitrogen represent a decreased phthalein and decreased indices of urea excretion. For instance, there is a patient in uræmia with 343 mgm. of urea per 100 Cc. of blood, whose index is less than 1 per cent. and whose phthalein is 0 per cent. Here is another 111 mgm. urea nitrogen per 100 Cc. blood, index of 4.2 per cent., and 2.4 per cent. for phthalein.

Now it is not unlikely that this particular patient, who has a relatively high urea figure in the blood, with no indication of disturbance of renal excretion, was a patient on a rather high proteid intake at the time of that observation and in whom there was a considerable amount of nitrogenous material in the blood because of the high nitrogen intake. The excess balance in the blood went out into the kidney, and the index of excretion was essentially a normal one, and that is borne out by the phthalein figure being pretty nearly normal. You see, these figures usually correspond pretty well. As the index drops the phthalein drops. One may go down 5, 10, or 15 degrees lower than the other, but they usually go parallel.

Very often we have high figures of urea excretion, perhaps 250 per cent. Some normal people apparently have fairly high ones, but usually those high figures indicate abnormality. Just what happens is not very well understood. We have had some individuals over 600 per cent., whereas the normal is 100 per cent. It probably represents some sort of hyperirritability or hyperpermeability of the kidney and renal disturbance, but we do not understand it very well, so at present we pay attention to decreases in the urea index as indicative of disturbance in renal function, and assume that the high figures probably also indicate disturbance in renal function, but that point is not so well understood.

STUDENT: Could those high indices that you get be considered as indicating something causing an irritation that might later go on to nephritis?

That is probably true. We regard it as a stage of hyperpermeability or hyperirritability, and often later have lower figures. We have accumulated some evidence in our work here for that, inasmuch as we have seen some cases with high indices suddenly drop to lower figures following fatigue from diuresis. We had one patient whom

I recall with a figure of 270 per cent. as an index. It was a cardio-renal case. She was given theocine and passed about 11 litres of urine in a diuresis, and 24 hours after that the index dropped down to 22 per cent., which would suggest that this high figure indicated renal damage, hyperirritability, and with the very heavy amount of work falling on that kidney it excreted much more than was to be expected. Following the diuresis, the figure dropped down to 1, which for the time being would be one indicating a very considerable renal disturbance. The urine, as we know, was that of a patient who had a moderate degree of nephritis, but essentially the entire condition was due to a cardiac condition. Those high figures are not thoroughly understood.

There is another factor that comes in and which has not been taken into account sufficiently, and that is the relation of the amount of water and the rate of flow of water and the rate of flow of urine. To get around that we have followed the practice, as McLean has done also, of adding about 150 Cc. or 200 Cc. of water an hour or so before the blood is taken in order to get a pretty free diuresis, and of discarding cases as unsatisfactory observations when you did not get a good diuresis. When you get very small amounts of fluid apparently in a normal individual the index does not run out quite so definite to an average constant figure, and that brings in the possibility of error or more fatigue in one case than the other from the adding of 150 to 200 Cc. of water, and probably has an effect in leading to these abnormally high indices. We have observed an index here, I think, of 960 in one case, but we were never quite sure whether that was an error in observation or whether it was due to an abnormal relation between the water and the urine. You can readily see that in order to get urea out in the urine you have got to have a certain amount of water and there must be some definite relation between the flow of water and the urea, and, of course, that formula takes into consideration the rate of excretion of urea expected in 24 hours of urine, but it does not make complete allowance for that, and that part of the problem is not understood completely. It is a method distinctly helpful in evaluating those cases where there is a normal phthalein output and in which we do not have any accumulation of nitrogenous substances in the blood, but we may have a decreased index of urea excretion as indicating some lesion, and it is particularly helpful in those

cases which have no particular evidence of renal disturbance other than the rather high blood nitrogen figures.

STUDENT: How much would that index vary in the same person in two different specimens?

Well, for instance, if 100 per cent. is normal, 80 to 120 per cent. would not be infrequent variations in the same individual. If a normal individual excretes within the two hours of observation approximately the same amount of urine, and there is no particular variation in the fluid, the figures from day to day run quite close together. In a patient with a damaged kidney, if there is any improvement, the curve of the index of urea excretion comes up pretty steadily. We consider below 80 or above 120 abnormal, so that leaves 40 spaces free for variations. The same individual might vary from 80 to 120 from day to day, but McLean's figures have run close together, observing the same individual on different periods, the same periods, etc. We have not observed normal individuals here.

STUDENT: What I do not see is why in the two-hour periods the concentration in the urine should differ.

Well, the concentration of the urine usually varies inversely with some other factor, and that is what keeps it pretty closely normal. That is, if the intake of water is decreased, we have a decrease in the urine and an increase in the concentration, and those things keep pretty well balanced. Every now and then we get a discrepancy, and we are up against the problem of whether the error is in the determination of the blood urea or the amount of urea in the urine or the measurement of the urine. There are a good many possibilities of error, but the phthalein output serves rather well as a check, because they ought to fluctuate together, but there are a good many cases that are practically normal, so far as the phthalein is concerned, that have lowered indices of excretion. Another advantage of the test is that it does not require any special diet and it does not make any difference whether the patient is nauseated and vomiting, provided he does not vomit during the test and does not swallow fluid during the test or does not have too small an output of urine.

The other test that I want to refer to briefly is useful in these cases and also useful to us because in a simplified form it can be very easily carried out with collection of the urine in two-hour portions from day to day, and the determination of the *specific gravity of the*

urine in these two-hour portions with the amount of sodium chloride and nitrogen, but especially the specific gravity. Some of these cases that show essentially a normal index of urea excretion and essentially a normal phthalein output show evidence of disturbance in renal function in fixation of the specific gravity and fixation of the sodium chloride and nitrogen. The principle of that test is that if a patient has three or five meals during the day, and those meals contain varying amounts of fluid and varying amounts of salt and varying amounts of nitrogen, at different intervals during the day the body is confronted with the problem of eliminating a considerable amount of fluid with a considerable amount of salt and relatively less nitrogen, and at another period relatively little fluid and a considerable amount of salt and nitrogen. The kidney normally accommodates itself to that presentation of different kinds of meal complexes by excreting a more or less concentrated urine, a urine with more sodium chloride, more nitrogen or less nitrogen, pretty closely parallel with the intake. If the kidney is injured it does not accommodate itself so well and does not accommodate itself so promptly, so that curves representing these factors flatten out in proportion as the kidney is diseased.

Here is a curve from a patient who had persistent headaches, slight hypertension, slight changes in the urine, with a question as to whether the patient had nephritis of a sufficient degree to produce the headaches or whether the headaches were more a type of nervous migraine. In the two-hour test, you see, the specific gravity varies. Her specific gravity varies here from 1.024 to 1.008 in the two hours immediately after that, so there is a very considerable variation in concentration as expressed by the specific gravity, and, as the concentration is influenced by the content of sodium chloride and nitrogen, those curves go up and down, probably not so much as in a normal individual, but there is pretty good function.

In contrast, here is the chart of a patient with more signs of chronic renal lesion, and her curves are more nearly straight lines. The specific gravity does not vary much in different periods, nor does the sodium chloride or nitrogen. This particular patient had periods of polyuria. There were large amounts of urine in some two-hour periods and small amounts in others, but the concentration remained the same. This individual did vary the amount much, but did not vary the concentration. These patients can not be compared

chart by chart as to amount, because they were on different diets. This patient was on a diet for nephritis of 75 Gms. of protein for three meals, and this patient was on a carbohydrate-free diet, because she also had diabetes. We studied the renal function in the midst of a diabetic diet. They illustrate a method of getting a very considerable amount of useful information without having the patient on a strictly fixed type of diet. Sometimes we put the patient on a low proteid diet and sometimes on a high proteid diet, with extras. To measure the specific gravity in the two-hour amounts, which practically anybody can carry out anywhere, simply involves collecting the urine in two-hour portions, and a great deal of information can be obtained from the fixation of specific gravity during the day.

Now, a case of severe nephritis usually day by day has a urine of about the same specific gravity. Such a patient in 24 hours will show no fluctuation in specific gravity. However, if a patient collects the urine in 24-hour periods, you might find the specific gravity relatively high or relatively low. The principle of the test is to test the urine more or less completely quite often. In feeding patients, if you let them eat what they want they will eat a different kind of meal for breakfast from that eaten for dinner or for supper, if that is the evening meal, without you bothering very much to supply them with directions for a variation. They take more fluid in the morning, and in the midday more proteid and sodium chloride, and the evening meal, if they are in the habit of having a pretty healthy dinner in the middle of the day, is a rather bland meal without an excessive amount of sodium chloride or nitrogen. The midday meal always contains vegetables, meat, etc., and a considerable number of purine bases which act as diuretics, so the usual diet would present enough variation.

Now a chart like this does not necessarily mean nephritis, but means a disturbance of renal function. A patient with an enlarged prostate and back pressure may have disturbance in renal function similar to that of a lesion in the kidney of the nature of nephritis, and *pernicious anœmia* cases we find practically always have a similar type of chart representing a two-hour test as cases of nephritis. For instance, very often they have pretty nearly straight lines. This patient with pernicious anæmia had a phthalein output of 70 per cent. and no albumin. Once he had a hyaline cast, but usually there

were no casts found, and yet for the two-hour test he showed a definite disturbance of his renal function just like a nephritis. In this particular case it was due to the fact that his hæmoglobin and number of red cells (that is, the quality of the blood) were sufficiently poor to interfere with the renal function. In cases of nephritis like this the renal function was interfered with by a lesion in the kidney—really an organic change in the vessels—or by organic lesions in the epithelium of the kidney, so that all of these tests should be interpreted in relation to your observations of the patient. It does not necessarily mean because the patient has a poor function that the individual has nephritis, but if nephritis is the cause of his renal function it tells you something about the severity of his nephritis. I do not know but that other conditions would show disturbance in renal function of this nature other than pernicious anæmia. Pernicious anæmia seems to be the very striking thing that does it, and other cases do not so frequently show disturbance. It is interesting in these pernicious anæmia cases that when the blood gets back to high figures the function improves, as shown by an irregular curve in the two-hour renal test, as the hæmoglobin and red cells have approached more nearly to normal.

All of these tests are useful in determining prognosis and, to a certain extent, treatment, and in some cases diagnosis, when there is a question of early nephritis, but they are mainly helpful from the point of view of prognosis.