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RENAL EFFICIENCY TESTS IN NEPHRITIS IN CHILDREN.\*

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IN the study of nephritis from the clinical standpoint, few have been the additions to our armamentarium for its better understanding since the time of Bright. It can, I think, be said that with the exception of the introduction of the instrument for the more accurate estimation of the degree of blood-pressure the physician of to-day approaches the study of a case of nephritis as did his predecessors of at least two, if not three or four, generations ago. If proof were required of this statement, such can be found in a comparison of the contents of the books on urine analysis supplied to the student to-day with what is found in the classical text-book on urine analysis published by Roberts in 1865, and in Reynolds' *System of Medicine*, published in 1879.

As the result of metabolism experiments, first instituted by Fleisher in 1881, for the better understanding of the diseased processes in nephritis, and continued by numerous workers during the succeeding years, definite information has been obtained regarding the ease or otherwise with which the various metabolic products are excreted by the kidney, and within recent years it has been suggested that by paying attention to these points the functional activity of the kidney can be gauged. It is in consequence of this that certain well-defined so-called renal efficiency tests have been devised, although it should be remembered that the physician has always given attention to the excretion of H<sub>2</sub>O not only with regard to the quantity but also to the time of its excretion after ingestion.

I feel that a certain unmerited distinction has been given to these so-called newer and more efficient methods of studying nephritis. Sir Andrew Clark, many years ago, pointed out the

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importance of paying attention to the specific gravity of the urine, and over twenty years ago Von Noorden stated that he had "never seen a case of acute nephritis in which increased diuresis was not at the same time accompanied by great increase in the elimination of residual excrementitious substances." The physician has always been taught to lay stress on the urinary output, and it may be because most of the cases that have come under my observation are by their nature accompanied by oliguria that I am not more enthusiastic about the help of these newer methods.

I do not mean to deny the importance of these advances in the better appreciation of the function of the kidney, but, as a clinician, I hold that they are outwith the sphere of routine urine analysis unless they make us to understand better the pathological processes from which the patient is suffering, to treat the individual case more efficiently and to prognosticate more accurately the outcome of the malady.

No one feels more acutely than does the clinician his limitations in these directions, and it was to test the practical value of these special methods that I commenced their practice about two years ago, the results of which I shall try to reveal to you to-night. There are several of these renal efficiency tests, viz. :—

1. Blood urea estimation.
2. Urea concentration test.
3. Urea concentration factor.
4. Ambard's co-efficient of urea concentration.
5. Chloride concentration.
6. Diastatic test, and
7. Various pigment tests.

In my study of this question I have selected three which are generally admitted to give a fairly comprehensive idea of the functional activity of the kidney, viz. :—

1. The phenolsulphonephthalein test.
2. The urea concentration test.
3. The urea content of the blood.

Before describing the various tests and detailing my results, I should say that my experience is limited to kidney disease as met with in a medical ward, and a medical ward in a Children's Hospital, so that all the patients were under 13 years of age.

They were all suffering from inflammatory lesions, no example of arterio-sclerotic kidney disease having been met with. I should also state that, although I am responsible for the observations on the urea concentration and the pigment tests, Dr. Strachan has invariably estimated the urea content of the blood, and he has kindly permitted me to use his findings for the present purpose.

I. *Pigment test.*—This test is carried out by administering intramuscularly 6 mgs. of phenolsulphonaphthalein, and estimating the amount excreted in the first two hours afterwards. The normal output is generally taken as from 60 to 85 per cent. Leopold and Bernhard<sup>1</sup> give a range of 50 per cent to 90 per cent, with an average of 70 per cent. Tileston and Comfort<sup>2</sup> give an average of 80 per cent, and Wilcox and Little<sup>3</sup> in a recent article on renal function place the average at 60 per cent in normal children. As the various writers give somewhat different figures for health, I carried out the test in a number (twenty-six in all) of normal children of various ages. In my experience the average output of pigment during the first two hours was 67 per cent, with a maximum of 85 per cent and a minimum of 56 per cent.

In 65 cases of nephritis I found that the excretion of pigment varied from 2 per cent to 94 per cent, with an average of 48 per cent in acute nephritis and 57 per cent in chronic nephritis. Wilcox and Little<sup>4</sup> give 5 per cent to 95 per cent as the variation, with an average of 10 per cent in acute and 40 per cent in chronic nephritis.

In acute nephritis the pigment excretion, although occasionally very high, was generally low at the onset, and as the severity of the symptoms subsided the excretion of pigment increased. Cases with a high pigment output at the beginning did not improve more quickly than those with a diminished excretion, therefore, the test was no guide to prognosis. Results of repeated tests during the course of the disease simply corroborated the improvement shown by the clinical symptoms and other tests. In chronic nephritis, *i.e.*, cases in which the condition had lasted for three months or longer, the test did not give any indication as to the progress or to the ultimate result; some cases with a high pigment output at every test

showing clinically no improvement, whereas others with a much lower output eventually recovered.

II. *Urea concentration test.*—This test was introduced a few years ago by MacLean and de Wesselow,<sup>5</sup> and they consider that in the majority of cases it gives more reliable information than any other. MacLean considers that it will detect a lesion of much slighter degree than can be done by estimating the blood urea. The *rationale* of the test is that after the ingestion of urea the blood urea rises, and if the kidneys are healthy a high concentration of the urine excreted in the first two hours afterwards results. If after the ingestion of 15 to 20 grammes of urea the urine of the second hour gives a concentration of over 2 per cent the kidneys are held to be fairly efficient, and the higher the concentration the more effective the kidney function. Urea sometimes causes diuresis in the first or second hour, and thus a vitiation of the test, and under these circumstances the period of observation is lengthened to three hours. If, however, the urea is given in the morning when no fluid has been taken for ten or twelve hours I find that diuresis seldom occurs.

In twenty-six children with apparently healthy kidneys the average urea content of the urine after 15 grammes was 3·7 per cent, the highest being 6 per cent and the lowest 2·3 per cent. In nephritis it varied from 1·2 per cent to 3·6 per cent, with an average of 2·1 per cent in acute and 2·8 per cent in chronic cases, so that although in many instances the readings fell within normal limits, in no case was the highest concentration obtained. The results of this test must, however, always be taken in conjunction with the urea content of the blood, as it is this which, as previously stated, determines the output. If taken alone, the readings may be very misleading. For instance, two cases of nephritis recently under my observation each gave 2·3 per cent as the result of the urea concentration test, and, without taking into consideration the urea content of the blood, this might have been taken as showing equally efficient kidney function; but the blood urea, which was estimated before any urea had been given, showed in the one case a concentration of 208 mgs. per 100 c.c., and in the other 24 mgs. per 100 c.c. This means that in the first case a "head" of urea in the blood of 208 mgs. per 100 c.c. was required before the kidneys were able to excrete 2·3 per cent of urea, whereas, in the second case, 2·3

per cent was excreted with a normal blood urea of 24 mgs. per 100 c.c. The first case was in the acute stage, with œdema, a diminished output of urine and a large amount of albumin. In the second case the acute symptoms had subsided, there being no œdema, and only a trace of albumin. Both children made a good recovery. In two other cases the urea concentration in the urine was 1.3 per cent, but in these the kidneys were not equally inefficient, as in the one case the blood urea was 23 mgs. per 100 c.c., and in the other 357 mgs. per 100 c.c. The former case recovered, the latter died.

III. *Blood urea.*—Although no one now believes that it is the retention of urea which is responsible for the toxic symptoms in nephritis, there is no doubt that in diseases, accompanied by impairment of the renal function, the urea content of the blood has a tendency to rise, apparently due to its non-excretion, a fact stated by Christison in 1829, and long looked upon as evidence of renal disease. As previously mentioned, this is an important deciding factor in the excretion of urea, other things being equal. The amount depends on the ingestion of protein.

The urea content of the blood in health is generally considered to lie between 20 and 40 mgs. per 100 c.c. Some writers give 15 to 50 mgs. per 100 c.c.; others say it may rise still higher and still be within normal limits. MacLean<sup>6</sup> considers that in young persons it lies towards the lower value.

I found that in twelve children with apparently normal kidneys it varied from 20 to 51.6 mgs. per 100 c.c., the average being 39 mgs. per 100 c.c.

In order to find what influence diet and time of day had on the urea content of the blood, this was estimated at four-hourly periods from 12 noon till 12 midnight. In those cases where it was found impossible to get four samples of blood, a sample was obtained both immediately before and one hour after a meal in both normal and nephritic children, on purely milk and on a mixed diet. In the normal child the blood urea generally fell at midnight, whereas in nephritis it either remained constant or was somewhat higher at midnight than during the day. In the normal cases it was higher one hour after than immediately before the meal, while in nephritis it was, as a

rule, higher before the meal than one hour after. In all cases, however, the variation was slight.\* We also estimated urea content of the blood after the ingestion of 15 grammes of urea, and found that the rise was almost the same in the normal and in the nephritic child, while the urea in the urine was much more quickly excreted in the normal than in the nephritic case.

In acute nephritis the average urea content of the blood was 76.6 mgs. per 100 c.c., the highest being 35.7 mgs. per 100 c.c., and the lowest 22.8 mgs. per 100 c.c. In chronic nephritis the average was 37 mgs. per 100 c.c., with a maximum of 69 mgs. per 100 c.c., and a minimum of 21 mgs. per 100 c.c. In acute nephritis the blood urea was generally high at the onset of the disease and diminished as the condition improved, but remained high in acute fatal cases, although in some acute cases it was normal.

In cases first coming under observation with symptoms of uræmia this test was no guide to prognosis, nor was it commensurate with the severity of the symptoms. In one case, admitted with headache and vomiting, whose blood urea was 208 mgs. per 100 c.c., the symptoms quickly subsided, and the child was well in six weeks; another, admitted with convulsions and coma, whose blood urea was only 66 mgs. per 100 c.c. died, within thirty-six hours of admission; and a third, also admitted with convulsions, had a normal blood urea of 40 mgs. per 100 c.c.

The results of the various tests have been summarised in tabular form below (Table I). It will be observed that in the table the percentage of abnormal findings with the individual tests (taking 60 per cent as the minimum for pigment excretion, 2 per cent as the minimum urea concentration, and 40 mgs. per 100 c.c. as maximum normal blood urea content) has been noted in both acute and chronic nephritis.

Although the absence of definitely pathological findings in the children who were clinically free from renal disease would suggest that these tests might be of value in the diagnosis of nephritis, the low percentage of pathological findings in patients suffering from definite renal disease refutes any such claim.

\* In normal cases the minimum increase was 2 mgs. and the maximum 9 mgs. per 100 c.c. of blood, whereas in nephritis the minimum was 4 mgs. and the maximum 13 mgs. per 100 c.c.

The same fact, also, disposes of their use for deciding if a cure is complete or not, as has been suggested by some workers. In this opinion we find ourselves in harmony with Osler,<sup>7</sup> who states that "after employing various tests in the hope of testing the functional ability of the kidneys the results have been that, although in some cases of uræmia one finds the expected accumulation of urea in the blood, in others the

TABLE I.—SUMMARY OF RESULTS OF DIFFERENT TESTS IN HEALTH, ACUTE AND CHRONIC NEPHRITIS.

	PIGMENT TEST PER CENT.			UREA CONCENTRATION TEST.			BLOOD UREA MGS. PER 100 C.C.		
	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.	Av.
Healthy Children (own observations),	85	56	67·1	6·0	2·3	3·6	51·6	20·0	39·2
Reputed Normal,	85	60	...	...	2·0	...	40	20	...
Acute Nephritis,	94	21	51·0	3·6	1·2	2·07	357·0	22·0	73·0
Percentage of Pathological Findings,	...	70%	...	...	44%	...	...	70%	...
Chronic Nephritis,	66	50	57	3·5	1·5	2·3	69·7	21·0	36·3
Percentage of Pathological Findings,	...	50%	...	...	50%	...	...	20%	...

TABLE II.—SELECTION OF CASES FROM SERIES CONTRASTING CLINICAL FINDINGS WITH RESULTS OF RENAL EFFICIENCY TESTS AND SHOWING TERMINATION.

Age.	Duration of Illness.	Edema.	Albumin.	Blood.	Casts.	Blood-Pressure Systole.	Pigment	Urea Concentration Test.	Blood Urea.	Result.
5 $\frac{3}{12}$ yrs.	10 days	+	+	+	+	100	33	1·7	30·4	Improved.
7 $\frac{9}{12}$ yrs.	7 days	+	+	+	+	-	94	1·7	45·0	Recovered.
5 $\frac{6}{12}$ yrs.	7 days	+	+	+	+	118	2·1	1·3	357·0	Died.
10 $\frac{7}{12}$ yrs.	11 days	+	+	+	+	150	30	3·0	40·5	Recovered.
7 yrs.	21 days	+	+	+	+	-	80	1·6	52·2	Recovered.
4 yrs.	7 days	+	+	+	-	80	30	2·3	99·9	Recovered.
7 yrs.	10 days	+	-	-	-	130	46	3·1	103·0	Recovered.

kidneys are, judged by those tests, normal. In some cases of nephritis, without any signs of uræmia, the kidneys are apparently as insufficient as in the worst uræmia cases."

Perhaps, however, the most striking feature of the investigation is the variable results of the tests in any individual case—in one patient the excretion of pigment was impaired; in another the power to concentrate urea; and in still another the retention of urea, as evidenced by the high blood urea, would be the only abnormality. These points are exemplified in Table II, in which the clinical findings and the results of the three tests are shown in a selection of the cases observed.

There is no doubt that by invariably employing all the different tests some abnormality would be found in a larger proportion of the cases examined, but, of course, this is quite evidently outside practical politics.

#### CONCLUSIONS.

The conclusions we have come to regarding these tests are—

1. That at the onset of the disease they do not give any more definite evidence of the severity of the case than do the clinical symptoms.

2. That they do not give any indication as to the ultimate result.

3. That during the course of the disease they merely corroborate the clinical symptoms.

4. That they do not help in deciding if the case is cured; and

5. That they are not of any help in differentiating between acute, subacute, and chronic nephritis.

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#### REFERENCES.

- <sup>1</sup> Leopold and Bernhard, *Amer. Journ. of Dis. of Child.*, 1916, vol. ii, p. 432.
- <sup>2</sup> Tileston and Comfort, *Amer. Journ. of Dis. of Child.*, 1915, vol. x, p. 278.
- <sup>3</sup> Wilcox and Little, *Amer. Journ. of Dis. of Child.*, 1923, vol. xxvi, p. 195.
- <sup>4</sup> *Ibid.*
- <sup>5</sup> MacLean and de Wesselow, *Brit. Med. Journ.*, September, 1921, p. 431.
- <sup>6</sup> MacLean, *Brit. Med. Journ.*, September, 1921, p. 431.
- <sup>7</sup> Osler, *Principles and Practice of Medicine*, 1911, p. 685.