The Journal of the American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. LXIV, No. 23

CHICAGO, ILLINOIS

JUNE 5, 1915

THE PHENOLSULPHONEPHTHALEIN TEST IN CHRONIC NEPHRITIS*

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Ever since Schlayer and his co-workers elaborated their system of differential renal function testing, much attention has been given to the subject of kidney function tests in nephritis. Clinical requirements demand not only that such a procedure shall be simple and easily available for clinical employment, but that it shall be of demonstrated accuracy; otherwise it may lead to faulty deductions in prognosis and possibly to blunders in diagnosis. However attractive it may appear from the pathologic point of view, to estimate the degree to which the different anatomic elements of the kidney are involved, it would seem that the mixed type of nephritis encountered clinically practically disposes of the attempt to weave fine diagnostic distinctions about the reactions secured by differential function tests. With clinical nephritis of the simplest type, there is enough general structural involvement to make conclusions as to special function involvement hazardous.

Many considerations render the study of renal function in detail an extremely complex problem. To base conclusions on differential tests assumed to reveal glomerular, tubular or vascular impairment necessarily implies that we can test the individual functions of the kidney, and presupposes a much more definite knowledge of the physiology of that organ than we in fact possess. Moreover, it is only in acute fatal cases of nephritis that anything like pure system involvement—glomerular or tubular—exists. As the matter stands, the only methods available for clinical usage are such as furnish information regarding the total function of the kidneys—their general excretory capacity.

THE PHENOLSULPHONEPHTHALEIN TEST

Tests for estimating general renal efficiency have consisted mainly of the introduction of various dye substances, which are excreted more or less completely in the urine. General agreement accords first place among these tests to the phenolsulphonephthalein test of Rowntree and Geraghty,¹ introduced in 1910. It was at first employed most extensively in surgical cases, especially with reference to the question of

operations on the urinary organs. It is equally applicable to medical cases, but the results are considerably more difficult of interpretation, and it is only recently that sufficient observations have accumulated to give it a fixed status in this class of cases. The harmlessness and simplicity of the test render it an easily available clinical procedure. In its application to nephritis Rowntree and Geraghty have shown from careful clinical and pathologic studies that the amount of phenolsulphonephthalein excreted varies as a general rule in rough ratio with the extent of the renal damage. In fatal uremia only traces or none at all of the dye appear in the urine for the two-hour interval, while in mild and moderate grades of nephritis the amount recovered from the urine may be normal or nearly so. These authors assert further that in cardio-renal cases when the heart is failing and the kidneys become passively engorged, a low phenolsulphonephthalein output is observed at first, rapidly rising subsequently as the heart action improves and venous engorgement subsides. An increase in the phenolsulphonephthalein index in such a case may be the earliest sign of restoration of compensation and represents a favorable prognosis. *Per contra*, a low excretory capacity, persisting after clinical evidence of cardiac improvement, points to a severe nephritis and a less favorable prognosis.

The authors of the test emphasize the purely empiric character of the investigation, owing to our lack of sound information as to the physiology of urinary secretion, and while attaching a high degree of prognostic value to its findings when positive and clear cut, they warn against too general prognostic interpretation, inasmuch as the test yields information only so far as renal efficiency or inefficiency can be estimated, whereas death may occur in chronic nephritis from many other factors, cardiac and cerebral in particular, concerning which the test gives little if any information. This method in common with other function tests must in consequence be considered always in conjunction with general clinical study; otherwise prognosis is made dependent on laboratory technic, which is always a hazardous alternative.

Coincidentally with the investigation of the functional adequacy of the kidneys in nephritis, attention has been directed to the estimation of the incoagulable or nonprotein nitrogen of the blood as offering a valuable means for securing information of prognostic value. Studies of this nature are particularly to be desired in the investigation of nephritis, since urine analysis cannot reveal the stage of accumulation of waste products, an accumulation that may vary from almost normal figures to enormous increase in uremia.

* Read before the Chicago Society of Internal Medicine, March 22, 1915.

1. Rowntree, L. G., and Geraghty, J. T.: Jour. Pharmacol. and Exper. Therap., 1910, i, 579; *ibid.*, 1911, ii, 393; The Phthalein Test—an Experimental and Clinical Study of Phenolsulphonephthalein in Relation to Renal Function in Health and Disease, Arch. Int. Med., March, 1912, p. 284.

THE INTERPRETATION OF RESULTS

Although the technic for nonprotein nitrogen determination offers no difficulties to the well-equipped chemical laboratory, it is so technical and time-consuming as to be beyond the capabilities of the clinician for routine employment. Studies of renal efficiency by the phenolsulphonephthalein test consequently offer great advantage as to convenience and ease of application. The chief drawback attaching to this method of estimating kidney permeability lies in the interpretation of results, for it is quite conceivable that the rate of elimination of a foreign dye substance may bear no definite relationship to the efficiency of the kidneys in excreting metabolism products.

Cases have been reported (Foster,² Baetjer³) in which the phenolsulphonephthalein test gave practically normal figures, yet fatal uremia resulted shortly after the tests were made.

Rowntree, Fitz and Geraghty⁴ assert that phenolsulphonephthalein is excreted solely by the tubular epithelium, a contention supported by Potter and Bell⁵ from their studies of experimental tartrate nephritis and it is conceivable that these reported cases may have been nephritis of predominantly glomerular type.

Such excretory paradoxes emphasize the loopholes for error in any general interpretation, however firmly the rule may appear to be established by results. The same thing is true of nonprotein blood nitrogen estimations in nephritis, a number of instances being reported in the literature, of uremia developing in the face of normal waste nitrogen content. However obscure and against the rule such exceptions may be, they serve to establish a discount against too rigid interpretation of any routine investigation. They serve to accent our ignorance of the exact nature of uremia and leave open the question of whether so profound a disturbance of the entire metabolism as results from severe nephritis there may not be some other factor, in addition to the action of urinary retention bodies, which is as yet unappreciated.

As the nonprotein index in the blood is admittedly the most reliable criterion of renal efficiency, it is desirable to correlate the elimination of phenolsulphonephthalein with the actual retention of nitrogenous waste in the blood. This has been undertaken by Frothingham, Fitz, Folin and Denis⁶ in experimental uranium nephritis. The results of their investigation demonstrate that in general the tests parallel each other as indicators of renal function, varying from normal during the course of the nephritis and returning to normal as the nephritis heals, with this important difference, that, whereas the amount of phenolsulphonephthalein excreted shows the renal function at the time of the test, the amount of nonprotein nitrogen of the blood measures the accumulating difference between the production of waste nitrogen bodies in the metabolism and the quantity excreted.

The time element — the duration of the nephritis — becomes, therefore, an important factor in the result.

It has long been known that during the course of any nephritis there are certain periods when the urinary constituents are normal in amount as compared with the intake, and other periods when they may be increased or decreased. These functional eccentricities of the kidneys, imperfectly understood, may have a bearing on some of the inconsistencies of excretory tests. Frothingham and Smillie⁷ carried out a series of observations on the nonprotein nitrogen and the phenolsulphonephthalein excretion in seventy-seven cases of chronic nephritis. From their charts it appears that the phenolsulphonephthalein excretion steadily falls as the amount of nonprotein nitrogen of the blood increases, phenolsulphonephthalein practically ceasing to appear in the urine when the nonprotein nitrogen reaches 100 mg. (four to five times normal). In a moderate number of cases a surprisingly low phenolsulphonephthalein output was shown for which no cause could be found, either from clinical findings or laboratory tests. They consider it fair to state that a considerable individual variation above and below the expected average may occur with the phenolsulphonephthalein test for which no explanation can be found.

In the main, the relation between nonprotein values and clinical findings is fairly exact. No nonnephritic cases showed accumulation. All their cases with nonprotein nitrogen above 50 mg. per 100 c.c. of blood gave clinical evidence of severe nephritis. In some of these cases the phenolsulphonephthalein excretion was unexpectedly good. On the whole, however, the nonprotein nitrogen varied inversely with the excretion of phenolsulphonephthalein in the urine. The accumulation of waste nitrogen seemed to be much less influenced by cardiac and other complicating factors than was phenolsulphonephthalein excretion.

Agnew⁸ undertook studies to determine what relation, if any, existed between phenolsulphonephthalein output and nonprotein nitrogen of the blood. He concludes that, in general, cumulative phenomena occur only when the excretion of phenolsulphonephthalein falls below 40 per cent. in two hours. This is in keeping with the observations of Folin, Denis and Seymour.⁹ Tileston and Comfort¹⁰ found that cases of chronic nephritis without symptoms of uremia showed normal or only moderate cumulative signs, the uremic cases, on the contrary, yielding a great increase in the nonprotein blood nitrogen, the excretion of phenolsulphonephthalein being roughly proportionate to the degree of retention.

Rowntree, Fitz and Geraghty⁴ show that chronic passive congestion of the kidneys gives rise to reduced secretion of phenolsulphonephthalein in the urine, without marked increase in the incoagulable nitrogen of the blood, and Agnew⁸ has been able by this contrast to separate cardiac from chiefly renal involvement. Foster¹¹ points out that while this holds true

2. Foster, Nellis B.: Functional Tests of the Kidney in Uremia, Arch. Int. Med., October, 1913, p. 452.

3. Baetjer, William A.: Superpermeability in Nephritis, Arch. Int. Med., June, 1913, p. 593.

4. Rowntree, L. G.; Fitz, R., and Geraghty, J. T.: The Effects of Experimental Passive Congestion on Renal Function, Arch. Int. Med., February, 1913, p. 121.

5. Potter, A. C., and Bell, E. T.: Am. Jour. Med. Sc., 1915, cxlix, 236.

6. Frothingham, Jr., C.; Fitz, R.; Folin, O., and Denis, W.: The Relation Between Non-Protein Nitrogen Retention and Phenolsulphonephthalein Excretion in Experimental Uranium Nephritis, Arch. Int. Med., September, 1913, p. 245.

7. Frothingham, Jr., Channing, and Smillie, Wilson G.: The Relation Between the Phenolsulphonephthalein Excretion in the Urine and the Non-Protein Nitrogen Content of the Blood in Human Cases, Arch. Int. Med., October, 1914, p. 541.

8. Agnew, J. Howard: Comparative Study of Phenolsulphonephthalein Elimination and Incoagulable Nitrogen of the Blood in Cardiorenal Diseases, Arch. Int. Med., March, 1914, p. 485.

9. Folin, Otto; Denis, W., and Seymour, Malcolm: The Non-Protein Nitrogen Constituents of the Blood in Chronic Vascular Nephritis (Arteriosclerosis) as Influenced by the Level of Protein Metabolism, Arch. Int. Med., February, 1914, p. 224.

10. Tileston, Wilder, and Comfort, C. W.: The Total Non-Protein Nitrogen and Urea of the Blood in Health and in Disease as Estimated by Folin's Methods, Arch. Int. Med., November, 1914, p. 620.

11. Foster, Nellis B.: Uremia. The Non-Protein Nitrogen of the Blood, Arch. Int. Med., March, 1915, p. 356.

for lesser grades of circulatory embarrassment, it might not prove a reliable criterion in the severest types of purely circulatory disturbance in which nonprotein nitrogen accumulation is not infrequently observed.

Thayer and Snowden¹² make an important contribution from the clinical side. These authors attempt to throw some light on the clinical value of the phenolsulphonephthalein test in prognosis by comparing their findings with the test and the anatomic alterations revealed at necropsy in fifty-four cases of nephritis of different types. In no instance of grave nephritis did they fail to find a material reduction in phenolsulphonephthalein excretion. Their study reveals a progressive diminution in the output of the dye, which they consider so definite as to give the test a considerable prognostic value. They conclude that there occurs in severe chronic nephritis a uniformly low phenolsulphonephthalein excretion, which, as a rule, in those instances not interrupted by an acute terminal process, decreases steadily up to the onset of uremia and is nearly or wholly suppressed from a day or two to a month before death. Acute terminal uremic developments which may be unsuspected clinically are common, and here a sudden diminution in the elimination of phenolsulphonephthalein may come on in cases in which the percentage previously excreted is not so low as to appear alarming. In not a single instance, and, indeed, not once in all their studies for five years, have these authors met with a good phenolsulphonephthalein excretion in a case of severe chronic nephritis. Their observations with the test in twenty cases of chronic passive congestion conform with the findings of Rowntree and Fitz,¹³ and they consider it clear that chronic passive renal congestion alone can result in marked reduction of phenolsulphonephthalein excretion, which may return to normal as cardiac compensation is reestablished.

VALUE OF THE TEST

The foregoing discussion briefly reviews the main facts brought out by investigation that furnish our warrant for the employment of this test in clinical practice. Accumulating clinical observation and the fact that results with the phenolsulphonephthalein test in the main parallel the estimation of nonprotein nitrogen of the blood encourage the belief that the findings are, within certain limitations, reliable for prognostic purposes. In interpreting its findings it is to be remembered that the test shows the functional power of the kidneys at the time of observation and for the dye only. The influence of passive renal congestion from cardiac causes is to be borne in mind. If excretory values are low and cardiac insufficiency be not present as a complicating factor, we should not disregard the warning simply because clinical indications of uremia are absent, and, on the other hand, if symptoms indicate danger, their significance is not to be neglected merely because phenolsulphonephthalein excretion approaches normal. Some experience with this test as a routine clinical procedure covering a period of two years encourages me to believe that it constitutes a method of value in nephritis and high pressure states generally. In my observations I have found that excretory response to the test is on the

average higher in ambulatory cases tested in office practice than in hospital cases, and this irrespective of the clinical condition present. This is, perhaps, as might be expected, owing to the more general functional decline in patients confined to bed. A comparison of age with functional response would appear to confirm the observation of Miller and Cabot¹⁴ that the excretion of phenolsulphonephthalein grows progressively less with advancing years.

It is extremely doubtful whether the phenolsulphonephthalein test can be employed to any important extent in the diagnosis of nephritis. Routine observations with the method show an output well within normal requirements in the majority of cases classed as nephritis with good cardiac compensation. The latency of chronic nephritis is well known and the inadequacy of clinical observation alone accurately to gage the degree of renal impairment is granted by all experienced observers. Any method that will assist the clinician in obscure cases to arrive at a more accurate knowledge of the organic inroads on kidney secreting structure will consequently be welcomed. It may happen that the renal efficiency test may occasionally prove of service in this direction. Rowntree¹⁵ cites the case of a boy who prior to the function test was looked on as having diabetes insipidus, but who, after one phenolsulphonephthalein test, was recognized as having advanced nephritis verging on uremia, a diagnosis substantiated at necropsy two weeks later.

Recently the test was instrumental in contributing to the better diagnosis of a case under my own observation.

The patient, a young man of robust habit and healthy appearance, complained of cardiac palpitation and vague precordial distress, with a sense of lassitude. Physical examination revealed a moderate degree of cardiac hypertrophy; blood pressure, systolic 160, diastolic 90. The urine was normal in all respects except for the presence of a very few hyaline casts. The best excretion index that could be secured with the phenolsulphonephthalein test was 30 per cent. in two hours. This was interpreted as giving a more serious aspect to his clinically latent nephritis than would have been indicated on clinical and urinary grounds alone.

Perhaps the most important service this test may render us in nephritis is in the diagnosis of obscure uremic conditions. During the course of any case of chronic nephritis there may arise gastro-intestinal, cerebral, visual or other functional disturbances, the uremic nature of which may be strongly suspected. Decisive action is necessary, although clinical grounds may be insufficient for a definite judgment regarding the uremic nature of the symptoms. Without loss of valuable time the phenolsulphonephthalein test will reveal promptly the degree of uræmia present.

A type of case that often presents some difficulties in diagnosis is so-called cardiorenal disease. In this condition the blood pressure ranges high, cardiac sclerosis is a prominent factor, and urinary signs signify that the kidneys share in the general arterial involvement. It is not always an easy matter to estimate the relative importance of the cardiac and renal moieties and to decide whether to regard the case from one or the other angle. I have found the renal sufficiency test of assistance in elucidating this point.

12. Thayer and Snowden: *Am. Jour. Med. Sc.*, 1914, cxlviii, 781.

13. Rowntree, L. G., and Fitz, R.: *Studies of Renal Function in Renal Cardiorenal and Cardiac Disease*, *Arch. Int. Med.*, March, 1913, p. 258.

14. Miller, Richard H., and Cabot, Hugh: *The Effects of Anesthesia and Operation on the Kidney Function, as Shown by the Phenolsulphonephthalein Test*, *Arch. Int. Med.*, March, 1915, p. 369.

15. Rowntree, L. G.: *Am. Jour. Med. Sc.*, 1914, cxlvii, 352.

My experience with the test would lead me to believe that it may prove of service when employed at periodic intervals in keeping track of the progress of a case and as a more accurate means of watching the effect of treatment than we possess by other means. By applying the test at intervals, the rise and fall in function index forms an interesting and possibly significant chart. How far we can trust the indications gained by routine observation of this sort is difficult to state, but there appears no obvious reason why we should not place some dependence on them. Rowntree and Geraghty report that if surgical patients were given careful preoperative treatment when the elimination of the phenolsulphonephthalein was dangerously low, a marked improvement in elimination occurred. It has been my experience that a steady improvement in the kidney function index may be expected following treatment in cases of nephritis not too far advanced. Mere rest in bed, strict diet and regulation of elimination will ordinarily effect such a result. In advanced cases bordering on uremia, it is rare to observe an improvement following treatment.

A point of possible importance to bear in mind in the interpretation of defective function response in chronic nephritis is the occasional existence of subacute exacerbations. The progress of many cases of chronic nephritis is punctuated by the occurrence of acute inflammatory phases resulting from intercurrent infections or severe kidney irritation. During the existence of such a phase, the excretion of phenolsulphonephthalein may be temporarily reduced much below average figures for the case, and for the time being low values may be observed. A case coming under observation at such a time may appear more grave when viewed from the standpoint of function response than might be justified by the subsequent progress of the case.

General experience with the test has verified the observations of Rowntree and Geraghty regarding the influence of passive renal congestion in interfering with phenolsulphonephthalein excretion. As is well known, contracted kidney cases and cardiorenal diseases generally are, during the later stages, to a large degree cardiac cases, the element of cardiac failure entering to a very important degree into the disabilities of the terminal stage. Broken cardiac compensation as a rule interferes very considerably with the excretion of phenolsulphonephthalein, values well below the safety line appearing with fair constancy along with cardiac edema in chronic nephritis and high blood pressure states. Unless we accord to the cardiac factor its due importance in this regard, we may be led erroneously to anticipate the advent of uremia, and to address our measures of treatment to the kidneys instead of to the heart as they should be.

In view of the clinical vagaries of chronic nephritis, which are notorious, it is perhaps not surprising to meet with glaring inconsistencies in the clinical application of this test. Cases that appear very grave on general clinical and urinary grounds are often found to yield a normal or nearly normal function index, and conversely, instances that appear to be on safe functional ground when judged by purely clinical findings, yield surprisingly low values when kidney efficiency is tested out. Just how we are to strike a balance between the two is often difficult to judge, but in view of the long recognized fact that it is impos-

sible to predict accurately by clinical study alone what course the disease will take in development, it would appear that we should at least accept the results of function study as a qualifying factor in prognosis. It is surprising how long certain cases of chronic nephritis will survive after the excretion of phenolsulphonephthalein is reduced to a mere trace or suppressed entirely; weeks and even months may go by before death ensues after this apparently terminal phenomenon has appeared. No absolute prognosis as to duration of life appears possible on functional findings alone, because we do not yet know how low the phenolsulphonephthalein excretion may go and yet be compatible with a renal efficiency sufficing to maintain life, provided the diet and hygiene of the patient are properly adjusted (Arnold¹⁶).

DIET THERAPY AND THE TEST

Diet therapy in nephritis is dominated by the principle of protein restriction. Our practice in this important item has hitherto been governed by empiricism without scientific control. So far as can be seen at the present time, the only reliable criterion available for regulating the protein intake in nephritis is the determination of the amount of waste nitrogen retention by blood analysis. That it is possible to reduce the urea waste nitrogen of the blood to normal or less is abundantly proved by the feeding experiments of Folin, Denis and Seymour,⁹ and of Frothingham and Smillie.¹⁷ Cases with a considerable retention require a restriction of protein, and by this means a return to normal may be brought about provided the azotemia be not too severe. In case of outspoken uremia no marked reduction of the azotemia results from a protein-free diet. Folin, Denis and Seymour state that the response to the phenolsulphonephthalein test can be reduced by one-half before abnormal accumulation of nonprotein nitrogen takes place in the blood. This estimate is in keeping with Agnew's statement that at 40 per cent., phenolsulphonephthalein excretion, cumulative phenomena appear in the blood. These observations may justify the assumption in clinical practice that when the response to the phenolsulphonephthalein test drops to 40 per cent. or lower in two hours, waste nitrogen blood accumulation is present.

Routine observations with this readily available test may thus enable us to appreciate with greater precision than is possible from clinical observation alone the point (40 per cent. or lower) where positive protein restriction becomes necessary. When the functional index is normal or nearly normal in contracting kidney, it is difficult to understand what harm will result to the kidneys, provided no inflammatory element is present, from a protein ration based on physiologic requirements. Aided by periodic functional testing to check up the functional integrity of the kidneys, and with our present knowledge of physiologic food requirement for good nutrition, the diet therapy of chronic nephritis may be adapted with reasonable safety, if not perhaps with accuracy, and with due realization that in so chronic and widespread a disease general nutrition and kidney conservation should stand on a parity.

30 North Michigan Boulevard.

16. Arnold: Boston Med. and Surg. Jour., 1914, clxx, 601.

17. Frothingham, Jr., Channing, and Smillie, Wilson G.: A Study of Different Nitrogenous Diets in Chronic Nephritis, Arch. Int. Med., February, 1915, p. 204.