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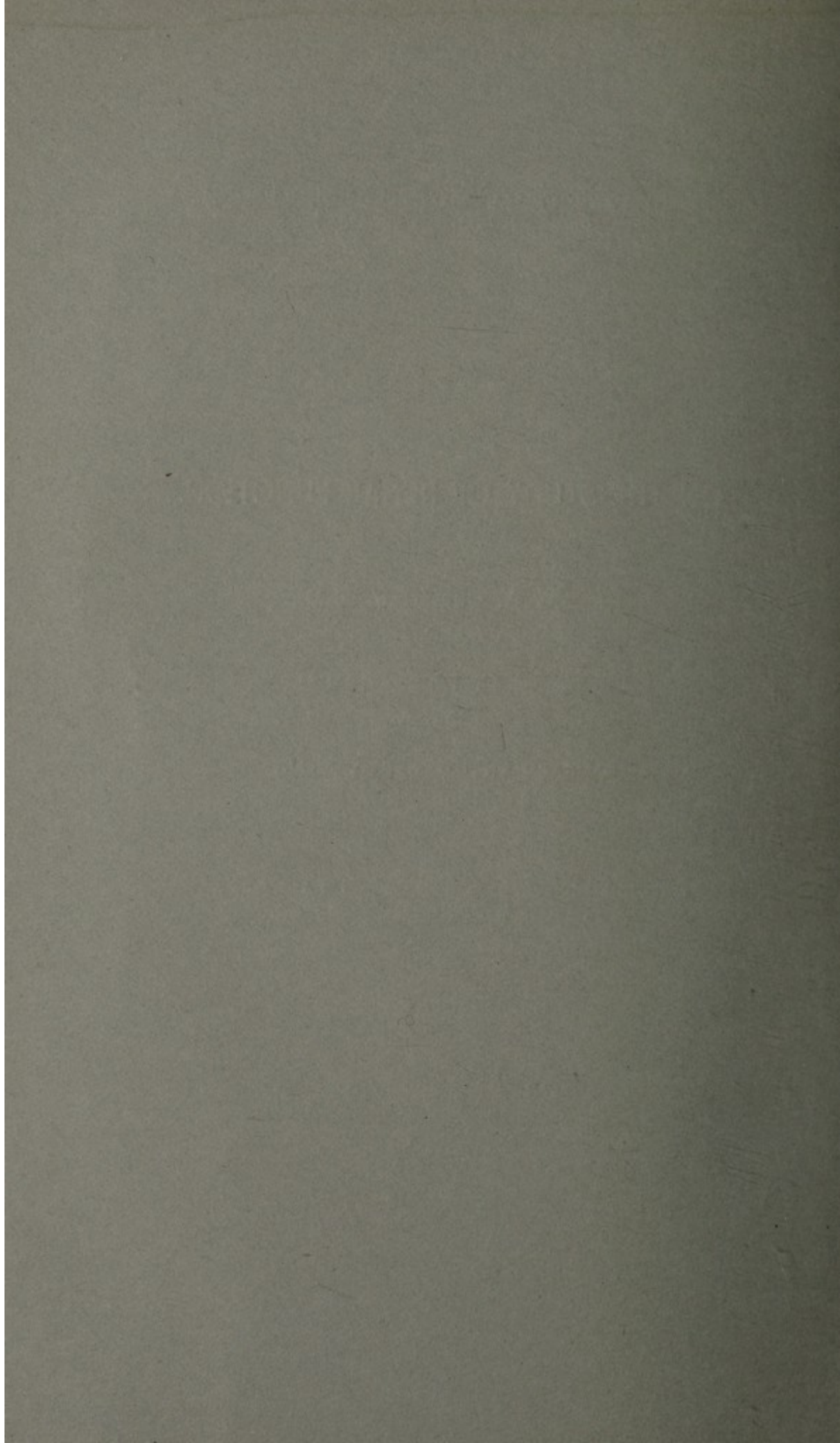
ON THE STUDY OF RENAL FUNCTION.

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ON THE STUDY OF RENAL FUNCTION: THE RELATION OF FUNCTIONAL TESTS TO PATHOLOGICAL DIAGNOSIS.

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The topic selected for discussion this afternoon, renal function, is one of interest to both physician and surgeon, for it deals with the means of measuring an excretory activity, necessary to life, of an organ subject to pathological changes in character diffuse, requiring medical management, or focal, demanding surgical operation. In either event, it is important to know, how well do the kidneys, combined or singly, function, and what has been the effect on function of remedial measures, for on this depends the prospects of continued life, or the risk of surgical treatment.

The problem of renal function has been one long under discussion and observation. The kidneys pouring their excretion, the urine, quite directly into the external world lend themselves readily to certain forms of study of their function, namely observation of changes occurring in the urine affecting the color, the reaction, the concentration, the character and quantity of various normal constituents, and the presence, qualitative and quantitative, of substances not found normally in the urine. At first crudely observed, these observations decade by decade have been made with increasing refinement of method.

Medical men in one way or another have long noted urinary variations, and from them have drawn inferences as to the health of the individual as well as inferences as to morphological changes in the kidneys. Much of the earlier work has concerned itself in the attempt to correlate urinary findings with renal morphology, to infer on the part of the clinician what lesions the kidney will reveal to the pathologist. Refinement of urinary analysis led to classification of variations in the urine, which in conjunction with observation of the patient's condition seemed to justify the diagnosis of different renal lesions. The pathologists, with improvements in technical methods, divided and subdivided renal lesions until a

very considerable knowledge of renal pathology was at hand for correlation with clinical conditions. Much was discovered by these methods, but the clinician, though able frequently to infer correctly the anatomical condition of the kidney, realized that there was often a considerable discrepancy between expected findings and observed conditions of the kidney; the clinician, though often correct in his diagnosis, too often failed and was confronted at autopsy by unexpected renal lesions. Even though the clinicians, for example, simplified the pathologist's morphological classification of types of nephritis to three groups, acute nephritis, chronic parenchymatous nephritis, and chronic interstitial nephritis, still mistakes in diagnosis were all too frequent and knowledge of that very important toxic manifestation of nephritis, uremia, has remained disappointingly slight, while prognosis in these cases was still more baffling. The pathologist investigated the end result in most cases; the clinician sought to harmonize a diagnosis of an end result with disturbances in function due to a lesion progressing at an unknown rate to this end result. Is it any reason for surprise that under these circumstances discrepancies between clinical and pathological diagnoses occurred?

This condition of affairs has led in recent years to renewed investigation, and the introduction of many new methods of determining renal function with the hope of correlating more satisfactorily functional disturbances with pathological lesions. It is primarily with these functional tests that we are concerned to-day, but by way of introduction it seems desirable to speak first of certain relations of these tests to the diagnosis of pathological lesions, and to leave to my colleagues the discussion of the relation of tests of renal function to prognosis and treatment.

In the present period of renal study the experimental work of Schlager and his associates in the medical clinic of Professor Romberg at Tübingen has been of great importance. They produced in rabbits acute renal lesions by injecting various substances known to cause injury to the kidneys. Instead of merely observing the morphological changes so produced at different intervals following the injections or in relation to doses of varying size, they investigated the effect of these substances on renal function.

They recognized the close relation existing between renal blood supply and general circulation, and the mutual effects of these on blood pressure. They did not lose sight of the interrelation between

vascular phenomena and function of renal epithelium with the dependence of diuresis on all of these factors. Consequently in their animals they observed general blood pressure, renal volume, diuresis, urinary variations, and renal histology. Instead of studying merely the changes produced in these factors by the renal irritants used, for this would have involved the uncertainty arising from an inability to measure several of these factors both before the renal irritant was given and again at the proper interval after its use, they compared the response of the kidney and circulation to various forms of stimuli. This involved the previous determination of the response in normal animals to such stimuli as tobacco smoke in the nostrils (sensory stimulus) and the effects of injections of adrenalin, salt, caffeine and phloridzin. Having, so to speak, standardized these responses, they sought by them, in addition to the methods of the direct observation of the urine mentioned above, to measure the disturbance produced by various toxic substances, chromium, uranium, mercuric chloride, cantharidin, arsenic, and diphtheria toxin.

The morphological effects of these substances had already been studied quite extensively by pathologists, and it was known that some produced very striking degenerative lesions of renal epithelium, while others had very much less effect on renal epithelium, and yet all led to the appearance of albumen and casts, not infrequently blood in the urine. With regard to renal function, Schlayer and his associates found that these toxic substances produced quite different effects. Some of them, as chromium and mercuric chloride, affected primarily the renal tubules and had little effect on the vascular apparatus (tubular nephritis), while others, such as cantharidin and arsenic, primarily caused vascular disturbances with little effect on the renal tubules (vascular nephritis). In the case of other toxic substances such as diphtheria toxin and uranium there was a condition produced at certain stages resembling in part a tubular nephritis, in part a vascular nephritis, with in general the tubular type in the early stages and a more marked vascular disturbance in the later stages. In the case of uranium there is a stage in which, though the renal vessels still react to stimuli, there is a sudden cessation of diuresis. It is particularly interesting that uranium, thus differing as shown by functional tests from other toxic substances, is the one substance which in animals frequently produces œdema, thus more closely simulating human nephritis.

In experimental toxic nephritis it was shown by Schlayer and his associates that the albumen may be excreted by either glomeruli or tubules; that cast formation occurs only in the tubules and that severe vascular disturbance causes decreased diuresis, though the reverse may not be true. Of the various observations made on rabbits, all may be applied in modified form to man except those on the volume changes in the kidney. However, vascular response is a very important factor in distinguishing functional types of nephritis, and so it became necessary to determine whether the excretion of different substances might not be used as a measure of the efficiency of the vascular or tubular apparatus to replace observations on renal volume which could not be made in man.

Though there was and still is considerable difference of opinion as to the physiological activity of various portions of the complicated renal structure, it is generally believed that certain normal constituents of the urine are the result of activity of definite portions of the renal structure. If this be true, then a defective elimination of one of these constituents indicates functional inefficiency of a certain portion of the renal structure, and so determines the localization of a functional, if not anatomical lesion. In the same way certain substances not normal constituents of the body were known to be excreted by the kidney without producing renal damage. Selective excretory activity of renal structures for certain foreign substances then might be utilized as further localizing tests of functional activity.

With the methods already used as functional tests of renal activity and the knowledge at hand of the types of functional disturbances produced by various toxic substances, variations in excretion of substances both natural and foreign to the body might be tested in relation to vascular and tubular types of toxic nephritis. This Schlayer and his associates did, using the excretion of water and lactose as a measure of glomerular activity and sodium chloride and potassium iodide as a measure of tubular activity. They found in experimental toxic nephritis in rabbits a close agreement between the excretion of these substances and the respective types of nephritis as determined by their earlier observations, thus confirming their views as to the place of excretion of these substances. This will serve to illustrate the method of using the selective excretory activity of portions of the kidney as a measure of forms of renal lesion and this method is not difficult of application to man.

However, as will be shown later, the place of excretion of these various substances as given by Schlager is not accepted by all.

Does the utilization of the method of testing renal function by measuring the excretory activity of the kidney for different substances throw much light on renal pathology in man? In relation to diagnosis of pathological lesions functional tests of the kidney might be expected to yield information on two points; first, are the kidneys diseased; second, what type of pathological lesion do they show? Do the functional tests yield these results?

Schlager and his associates found in acute nephritis predominatingly of the vascular type, a delayed excretion of lactose and a normal elimination of potassium iodide, a disturbance of water excretion and a normal salt elimination. They point out that oliguria does not necessarily occur in a vascular nephritis; in fact polyuria is more common but indicates a less marked vascular disturbance. Low concentration of the urine may be the result of tubular insufficiency, a failure to excrete salts (tubular hyposthenuria), or the result of increased glomerular excretion of water, vascular hypersensitiveness causing vascular hyposthenuria. Increased water elimination may exist with decreased lactose excretion, indicating a selective, excretory activity within the glomerulus. According to them vascular hypersensitiveness is a valuable index of vascular disturbance, and its persistence indicates a failure of the process to heal. In chronic vascular nephritis, in which they include the atrophied kidney of chronic interstitial nephritis, they find the same excretory relations of water, lactose, salt and potassium iodide. In the chronic forms, as in the acute, polyuria or oliguria may exist, depending on increased or decreased vascular sensitiveness. In neither acute nor chronic types is the amount of urine any measure of the kidneys' functional capacity.

They claim by these methods to be able to distinguish definitely certain types of acute and chronic nephritis (tubular nephritis, vascular nephritis), and to find their distinguishing characteristics to be quite sharply demarcated. If this claim is sustained, a definite advance in our knowledge of human renal lesions has been made. Of the cases studied by Schlager and his associates, but one died and had a post-mortem examination. Consequently it cannot be said that their cases have added any definite information that will help in anticipating during life what the microscopic study of the kidney will reveal after death. Still, if these methods give a sharply

outlined functional diagnosis, even without leading to a satisfactory anatomical diagnosis, a distinct gain has been made. What has been the experience of other observers using these tests?

Von Monakow, working in Müller's clinic in Munich, found, contrary to the observations of Schlayer, a delayed potassium iodide excretion with no disturbance of salt excretion. Furthermore, duration of potassium iodide excretion did not seem closely related to severity of renal disturbance. In four patients histological examination of the kidneys was made; here von Monakow, in agreement with Schlayer, found salt excretion to be normal or delayed according to whether the tubular epithelium showed no degenerative lesions or was definitely degenerated. Potassium iodide excretion was most delayed in the two cases in which a glomerular lesion was most prominent, which was not in agreement with Schlayer's claims. Nitrogen elimination, tested by giving weighed amounts of urea, von Monakow found delayed in cases with glomerular lesions. Contrary to Schlayer, von Monakow considers disturbance of water excretion dependent on tubular degeneration.

On the other hand in a group of cases studied by Conzen at Cöln, five came to autopsy. These were cases of chronic interstitial nephritis with heart hypertrophy and in them Conzen found the functional tests of Schlayer in agreement with the histological findings, for they indicated a vascular lesion and extensive glomerular changes were found.

Rowntree and Fitz consider that lactose is an index of the vascular function of the kidney, thus agreeing with Schlayer, though in another paper they show that in the*frog, at least, lactose may be excreted by the tubules. On the other hand potassium iodide, which Schlayer believes to be retarded in excretion by tubular lesions, they find retarded also in simple chronic passive congestion and so of no value in distinguishing renal from cardio-renal cases.

Rowntree and Fitz are unable to make the sharply marked distinctions between vascular, vasculo-tubular, tubulo-vascular, and tubular nephritis made by Schlayer and his associates on the basis of their functional tests. They agree with Schlayer that the mechanism of the excretion of lactose differs from that of salt and potassium iodide. Few of their cases came to autopsy and the kidneys were not studied with especial reference to correlating functional disturbances with pathological lesions.

Nonnenbruch studied the excretory relations of salt, water, lactose, and potassium iodide in passive congestion. He found these relations were often disturbed in passive congestion, but unlike cases of nephritis the disturbance was dependent on the excretion of water, and when this returned to normal the other substances were excreted normally. In this respect there was a distinct difference between function in passive congestion and nephritis.

The several investigations cited will serve as examples of this method of renal study. It is evident that different observers have not obtained constant results, and opinions as to locus of excretion of the several substances are not in accord. So far too few cases are recorded with these functional tests and subsequent histological examination of the kidneys to justify final conclusions, but such as are recorded do not seem to indicate that any very close correlation between function and anatomical lesion can be made on the basis of rate of excretion of such substances as lactose, potassium iodide, salt and water.

Perhaps this is not to be expected, for Schlayer and his associates pointed out that in experimental animals there was no anatomical lesion demonstrable in the kidneys to explain differences in vascular response to stimuli. Takayasu studied particularly the glomeruli and found but slight anatomical change to explain demonstrated disturbances in function. On the other hand we have found quite commonly in uranium nephritis in rabbits glomerular lesions which appear to have been overlooked by Schlayer and his associates. Still it is undoubtedly true that in the functional studies of experimental toxic nephritis anatomical lesions do not parallel closely functional disturbances and so from these studies it was to be anticipated that in man there would continue to be some discrepancies between clinical diagnosis, even though based on functional tests and demonstrable structural changes in the kidney. These particular functional tests have yielded valuable information, but so far they have failed to serve as an adequate basis of diagnosis of type of renal lesions. They have, however, given much aid in determining whether, in a given case, a nephritic lesion actually exists or not. When applied to our clinical work they will undoubtedly save us often from the mistake of not diagnosing a renal lesion when such exists, even though they do not tell us of what type that lesion is.

A slightly different method of studying renal function has been employed by Volhard in distinguishing during life four forms of atrophied kidney (*Schrumpfnieren*) in correspondence with two groups described anatomically by Jores. This method consists in measuring the ability of the kidney to excrete large amounts of water in a relatively short time, and to excrete large amounts of solids with small amounts of water. The normal kidney can excrete $1\frac{1}{2}$ litres of water in four hours, and on the other hand on a dry diet can concentrate the urine to a specific gravity of 1025-1030. By applying these methods along with observations of blood pressure and heart hypertrophy, and study of symptoms and other physical signs, Volhard distinguishes a red granular kidney or primary atrophic kidney, a secondarily atrophied kidney, a mixed form, and an atrophied kidney without heart hypertrophy.

Frey has reported from Gerhardt's clinic at Basel somewhat similar studies of 78 cases of chronic nephritis, 43 of which came to autopsy. In these cases he is able to make quite definite groupings according to clinical observations and functional tests which are similar to, though not identical with the groups made by Volhard. When these subdivisions, however, are put to the test of anatomical study of the kidney, the agreement is not very close, so that Frey is of the opinion that it is very difficult to make clinical subdivisions of the atrophied kidney which will correspond with anatomical subdivisions made on the basis of histological study of the kidney. A similar view has been taken by Krehl in discussing Volhard's original paper.

Phenolsulphonephthalein seems to play a similar rôle. It is a most valuable aid in determining any diminution in total renal function, but it does not seem to help much in diagnosing what type of nephritis exists. Rowntree and Geraghty found that in frogs phenolsulphonephthalein could be excreted by the tubules. The frog is used for these experiments because glomerular function can be excluded, owing to glomeruli having a vascular supply distinct from the tubules. Other observations indicated that in man phenolsulphonephthalein is mainly excreted by the tubules, but this localization of excretion does not seem to be selective enough for use in diagnosis of the type of pathological lesion in a case of nephritis.

In all the methods discussed up to now, renal function has been tested by measuring the ability of the kidney to excrete certain

substances which are supposed to be excreted by definite portions of the renal structure. In making anatomical studies of the human kidney to determine how far renal function may be correlated with the pathological lesion, it has not been possible to apply to the human kidney methods similar to the vital staining used in experimental animals. These vital stains have shown in animals a very great amount of differentiation in the epithelium lining the tubules and a very considerable degree of specificity of different toxic substances for these several kinds of renal epithelium. This limitation in method of studying the human kidney may explain some of the failure to correlate morphology with function.

Another important source of error may be in our failure to allow for variations in excretion not dependent on structural disturbances, hardly dependent on functional lesions, but due to variations in fatigue in the kidneys of different individuals, or of the same individual on different days. Amato and Flaggella have shown that in normal rabbits variations in excretion of those fed with salt and water are due to renal fatigue. Schlayer has pointed out that the injured kidney is abnormally easily fatigued. This fact opens to the above methods of testing renal function, the possibility of numerous errors in interpretation of results, even though fatigue itself may serve as a functional test of renal insufficiency.

The quantitative determination of the non-proteid nitrogen in the blood of nephritics has received more attention as a means of gaining knowledge of uremia than as a method of diagnosing the pathological lesion of the kidney. Strauss found that rest-nitrogen showed more variation in nephritis and uremia than did the molecular concentration of the blood as determined by measurements of the freezing point. Ascoli, Umber and others investigated phases of this problem with similar results. Recently Hohlweg has claimed that marked nitrogen retention was an index of renal insufficiency rather than a sign of uremia; if there was a high degree of nitrogen retention in the blood, it indicated a fatal issue with or without uremia; in the uremic stage nitrogen retention might not be excessive and then, according to Hohlweg, the prognosis was relatively good. Strauss in reply, points out that the term uremia is indefinite, and part of the difference between his views and those of Hohlweg are merely matters of terminology. Uremia, both agree, may occur without marked nitrogen retention. This is usually in cases with marked œdema or where the uremia is of the convulsive

or eclamptic type. In the former, hydremia reduces the amount of nitrogen in the blood, and in the latter the symptoms conceivably may be due to other factors than those producing the ordinary type of uremia.

Recently, Folin has devised methods of determining non-proteid nitrogen and other substances in blood and urine which require the use of only very small quantities, in the case of blood 2-5 cc. These methods make it possible to quantitate nitrogen bodies in the blood of patients with far greater ease and freedom than was possible by earlier methods that necessitated using relatively large quantities of blood. Folin and his associates have found, like the previous observers, a considerable nitrogen retention in cases of nephritis. Folin, Karsner and Denis in experimental acute nephritis produced in the cat by uranium, chromate and cantharidin, have found an accumulation of nitrogen in the blood. This is more marked in those forms of experimental nephritis of the vascular type than in the tubular type. Anatomical study shows distinct glomerular involvement in the cats with greatest retention. In the rabbit, Frothingham, Fitz, Folin and Denis have found a similar nitrogen retention in experimental uranium nephritis. They compared the nitrogen retention with the phthalein excretion and found the two methods of testing functional renal activity to give quite comparable results. As might be expected, phthalein excretion decreased quickly while a longer time was needed for nitrogen retention to take place. Similarly the nitrogen content of the blood remained high after phthalein excretion had risen toward the normal level. I have found in conjunction with Folin, high figures for non-proteid nitrogen in rabbits with severe uranium nephritis and these are particularly high in rabbits that in addition have received diuretin. In other studies in our laboratory we have found that diuretin and other diuretic drugs exert an unfavorable influence on severe acute experimental nephritis expressed in the shortening of the life of the animals and the severity of the lesion found on histological study. It is especially in these animals with nephritis, to which diuretic drugs have been given, that marked glomerular lesions such as have been described by myself and O'Hare occur.

Most of these observers have found a greater average nitrogen retention in cases of interstitial nephritis than in cases of parenchymatous nephritis. As already pointed out, von Monakow found nitrogen elimination following doses of urea was delayed in cases

with glomerular lesions. Experimental work as cited above harmonizes with the observations of von Monakow, for nitrogen retention appears to be most marked in nephritis of the vascular and tubulo-vascular type of Schlayer's classification. However, in Hohlweg's cases the averages for interstitial and parenchymatous nephritis are not very different and individual cases may show no difference, so it cannot be claimed from this work that any great help has been given in the diagnosis of types of renal lesion. However, finding a distinct nitrogen retention is often of very great help in distinguishing cases in which the symptoms are chiefly of renal origin from cases in which they have other causes, the very frequent association of high degrees of nitrogen retention with uremic conditions may be of the greatest diagnostic help in patients in whom it is doubtful whether cerebral manifestations are of renal origin or not.

Wohlgemuth's method of determining variations in urinary diastase has not been applied in the observation of cases with any special view of diagnosis of the type of renal lesion. The estimation of the indican in the blood as suggested by Obermayer and Popper has been discussed as an indication of uremia rather than as a diagnostic test. Variations in urinary acidity have been observed too, more as a measure of certain functional disturbances brought about by nephritis but not dependent on any particular form of anatomical lesion.

Early in this paper it was stated that in the diagnosis of pathologic lesions of the kidney functional tests might be expected to yield information on two points; first, are the kidneys diseased; second, what type of pathological lesion do they show? Review of the methods of testing renal function by measuring the excretion of salt, water, lactose, potassium iodide, and sulphonaphthalein, by measuring the retention of non-proteid nitrogen in the blood, by the determination of diastase in the urine, by determining the presence of indican in the blood, or by estimating urinary acidity, shows that very great aid is given in determining clinically whether the kidneys are diseased, but distinctly less help has come in answering the second query, what type of pathological lesion do the kidneys show. As in all forms of clinical diagnosis, not the single test but many yield the data on which diagnosis must be based. In this sense these functional tests have yielded new data and a discriminating evaluation of this new data along with a consideration of

data furnished by other methods of examining our patients already long in use, justify us in making diagnoses of renal condition with an increased certainty. We can expect fewer failures in renal diagnosis than before we had these functional tests, but so long as microscopic study fails to yield a demonstrable anatomical change to correspond with all observed functional variations, so long will we remain unable to make in advance an exact anatomical diagnosis which in most cases will prove to be correct when the pathologist examines the kidneys.

1. Experimentelle Studien über toxische Nephritis. Schlayer and Hedinger, Deutsch. Archiv f. klin. Med., 1907, XC, 1.
2. Über nephritische Ödem. Schlayer, Hedinger and Takayasu, Deutsch. Archiv f. klin. Med., 1907, XCI, 59.
3. Untersuchung über die Funktion kranker Nieren. Schlayer and Takayasu, Deutsch. Archiv f. klin. Med., 1909, XCVIII, 17.
4. Untersuchung über die Funktion kranker Nieren beim Menschen. Schlayer and Takayasu, Deutsch. Archiv f. klin. Med., 1911, CI, 333.
5. Untersuchung über die Funktion kranker Nieren. (Chronische vaskuläre Nephritiden.) Schlayer, Deutsch. Archiv f. klin. Med., 1911, CII, 311.
6. Beitrag zur Funktionsprüfung der Niere. v. Monakow, Deutsch. Archiv f. klin. Med., 1911, CII, 248.
7. Über Nierenfunktionsprüfung. Conzen, Deutsch. Archiv f. klin. Med., 1912, CVIII, 353.
8. Studies of Renal Function in Renal, Cardioresenal and Cardiac Disease. Rowntree and Fitz, Archives of Int. Med., 1913, XI, 258.
9. The Effects of Experimental Chronic Passive Congestion on Renal Function. Rowntree, Fitz and Geraghty, Archives of Int. Med., 1913, XI, 121.
10. Zur Kenntnis der Funktion der Stauungsniere. Nonnenbruch, Deutsch. Archiv f. klin. Med., 1913, CX, 162.
11. Über die Beziehungen zwischen anatomischen Glomerulusveränderungen und Nierenfunktion bei experimentelle Nephritiden. Takayasu, Deutsch. Archiv f. klin. Med., 1907, XCII, 127.
12. Vascular Lesions of the Kidney in Acute Experimental Nephritis. Christian, Archives of Int. Med., 1911, VIII, 469.
13. Glomerular Lesions in Acute Experimental (Uranium) Nephritis in the Rabbit. Christian and O'Hare, Jour. of Med. Research, 1913, XXVIII.
14. Ueber die funktionelle Unterscheidung der Schrumpfnieren. Volhard, Verhandl. d. Kongress f. innere Medizin, 1910, 735.
15. Über die Beziehungen d. Schrumpfnieren zur Herzhypertrophie v. path.-anatom. Standpunkt. Jores, Deutsch. Archiv f. klin. Med., 1908, XCIV, 1.
16. Zur Pathologie der chronischen Nephritiden. Frey, Deutsch. Archiv f. klin. Med., 1912, CVI, 347.
17. Krehl, Verhandl. d. Kongress f. innere Med., 1910, 762.

18. The Phthalein Test: An Experimental and Clinical Study of Phenol-sulphonephthalein in Relation to Renal Function in Health and Disease. Rowntree and Geraghty, Arch. of Int. Med., 1912, IX, 284.

19. Zur Morphologie die Nierensekretion unter physiologischen und pathologischen Bedingungen. Monograph. Suzuki, Jena, 1912.

20. Ueber Nierenermüdung. Amato and Flagella, Zeitsch. f. klin. Med., 1911, LXXII, 474.

21. Ueber die Ermüdbarkeit der Nierenfunktion. Schlager, Verhandl. d. Kongress f. innere Med., 1912, 501.

22. Über das Verhalten des Reststickstoffes des Blutes bei Nephritis und Urämie. Hohlweg, Deutsch. Archiv f. klin. Med., 1911, CIV, 216.

23. Der Reststickstoff in seinen Beziehungen zur Urämie und zur Prognose von Nephritiden. Strauss, Deutsch. Archiv f. klin. Med., 1912, CVI, 219.

24. New Methods for the Determination of Total Non-Proteid Nitrogen, Urea and Ammonia in Blood. Folin and Denis, Jour. Biol. Chem., 1912, XI, 527.

25. Nitrogen Retention in the Blood in Experimental Acute Nephritis of the Cat. Folin, Karsner and Denis, Jour. Exp. Med., 1912, XVI, 789.

26. Nitrogen Retention and Phenolsulphonephthalein Elimination in Acute Experimental Nephritis. Frothingham, Fitz, Folin and Denis, Arch. of Int. Med., 1913.

27. A Study of the Therapeutic Value of a Diuretic (Theobromine sodium salicylate or Diuretin) in Acute Experimental Nephritis. Christian and O'Hare, Archives of Int. Med., 1913, II, 517.

28. The Effect of Diuretic Drugs on the Life of Animals with Severe Acute Experimental Nephritis. Walker and Dawson.

29. Untersuchungen über d. Diastasen. Beitrag zum Verhalten d. Diastase im Urin. Wohlgemuth, Biochem. Zeitsch., 1909, XXI, 432.

30. Beitrag zum Verhalten der Diastase im Blut und im Urin beim Kaninchen. Hirata, Biochem. Zeitsch., 1910, XXVIII, 23.

31. Ueber Urämie. Obermayer and Popper, Zeitsch. f. klin. Med., 1911, LXXII, 332.

32. On the Intensity of Urinary Acidity in Normal and Pathological Conditions. Henderson and Palmer, Jour. Biol. Chem., 1913, XIII, 393.

33. On the Extremes of Variation of the Concentration of Ionized Hydrogen in Human Urine. Henderson and Palmer, Jour. Biol. Chem., 1913, XIV, 81.

THE STUDY OF RENAL FUNCTION: ITS BEARING ON TREATMENT.

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No advance gained in the knowledge of any group of diseases can be without significance for treatment. This is particularly true when new methods of study increase our understanding of the complex functional disturbances and afford more precise means for their differentiation. On the other hand, the possible gain to practical therapeutics depends primarily upon the existence of means for favorably influencing disordered function. In the domain of chronic diseases of obscure causation, which make up so large a part of the subject matter of internal medicine, diagnostic skill, inadequate though it be, usually runs far ahead of remedial measures.

Of no diseases is this more true than of the medical diseases of the kidney. Rowntree has shown how the added precision in functional diagnosis, gained by such a measure as the sulphone-phthalein test, has made the results of renal surgery more certain. From a broad standpoint, therefore, this functional test, and the less satisfactory ones which it has replaced, have contributed greatly to the effectiveness of treatment. But the medical diseases of the kidney, which we group under the contentious term nephritis, do not permit of so easy an attack after recognition. It is not conceivable that even the earliest discovery of functional disorder should lead to brilliant therapeutic results when the underlying lesions are essentially progressive, though we may hope to safeguard the damaged organ and retard to some extent the development of advanced anatomical changes. Only studies in the etiology of chronic disease and the discovery of means of prevention can ever make internal medicine as cheerful and therapeutically satisfying as surgery. At present, the internist cannot shift the responsibility for his "inoperable cases" to any other convenient shoulders.

Nevertheless, as the result of the recent studies of renal function, the internal treatment of renal disease has made definite progress along two lines:

(1) The study of experimental nephritis in animals has made clear the existence of isolated disturbances in the excretion of individual constituents of the urine, and the existence of definite types of abnormal reaction of the diseased kidney to stimuli. These have been found to have their counterparts in human nephritis.

(2) The accurate study of the salt and water exchanges in human nephritis and their relations to œdema, has resulted in a precise and scientific method of treatment which is highly effective in certain types of renal disease.

The study of disturbances in the excretion of individual urinary constituents in human nephritis as a guide to treatment is not of recent date. As early as 1881, Fleischer¹ conducted elaborate observations. Von Noorden and his pupils have been especially active in this field, and as a result of the facts which they accumulated, von Noorden² has formulated fairly definite rules for protective treatment in the various clinical types of nephritis. His most important practical contribution is the management of the water intake and his demonstration that the conventional milk diet for nephritis, while empirically successful, was irrational, because of excessive fluid volume and protein content. The diet which he has worked out for acute nephritis, with low protein content but ample fat and carbohydrate, of 1500 c.c. bulk, has been of great practical value.

The recent studies of Schlayer³ and his co-workers, especially Hedinger and Takayasu, have approached the problems of the functions of the diseased kidney from a more fundamental standpoint. They have observed in animals with various types of

¹ Fleischer, R., *Klinische und pathologisch-chemische Beiträge zur Lehre von den Nierenkrankheiten*, Deutsch. Arch. f. klin. Med., 1881, xxix, 129.

² von Noorden, Carl, *Clinical Treatises on the Pathology and Therapy of Disorders of Metabolism and Nutrition*, 1905, E. B. Treat & Co., translation.

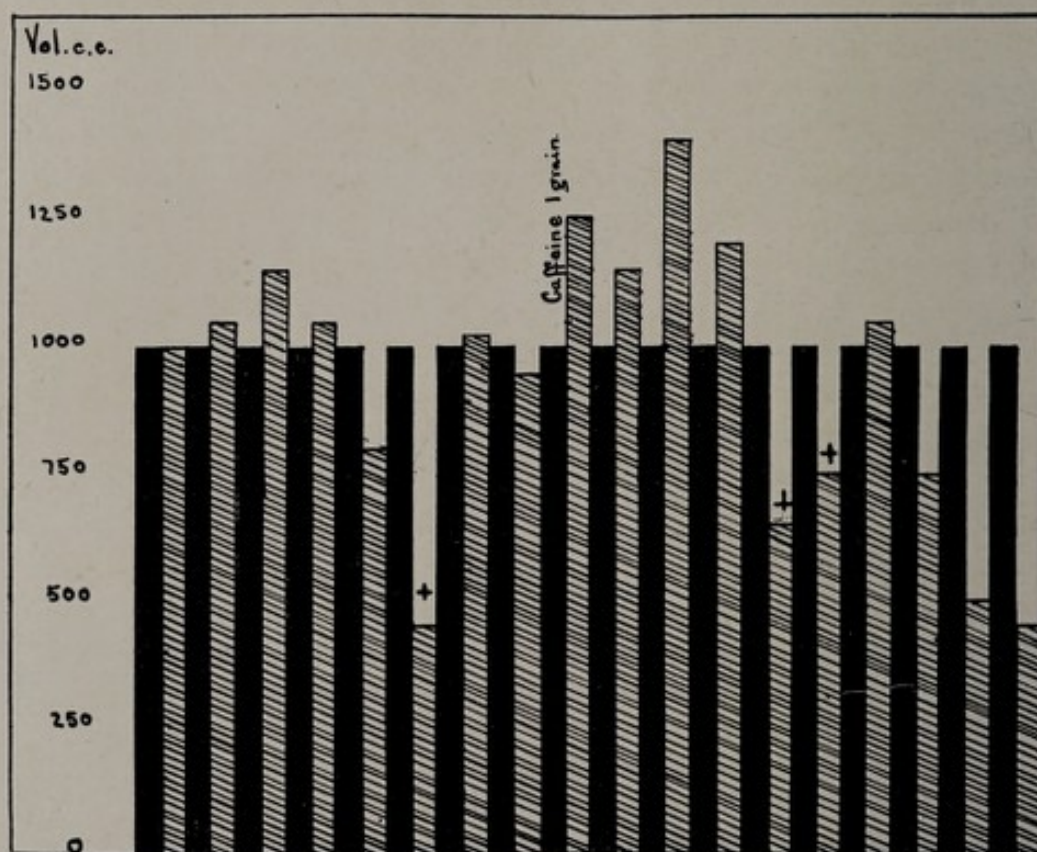
³ Schlayer and Hedinger, *Experimentelle Studien über toxische Nephritis*, Deutsch. Arch. f. klin. Med., 1907, xc, 1; Schlayer and Takayasu, *Untersuchungen über die Funktion kranker Nieren*, Deutsch. Arch. f. klin. Med., 1909, xcvi, 17; Schlayer and Takayasu, *Untersuchungen über die Funktion kranker Nieren beim Menschen*, Deutsch. Arch. f. klin. Med., 1910, ci, 333; Schlayer, *Untersuchungen über die Funktion kranker Nieren. B. Chronische vaskuläre Nephritiden*, Deutsch. Arch. f. klin. Med., 1911, cii, 311.

experimental toxic nephritis, the disturbances in the excretion of water and sodium chloride among the normal urinary constituents, and of potassium iodide and lactose as foreign test substances. They have studied equally the changes in the general blood pressure and the responses of the kidney vessels to various stimuli, including substances producing diuresis and excretion. This work they have more recently extended to the study of selected cases of human nephritis. While the results in the main bear upon the underlying problems of the pathology of nephritis and the sub-division of diseased kidneys into functionally separable types, as Christian has already set forth, nevertheless, some of their results must now be reckoned with in the treatment of human nephritis. In the first place, they have shown that, both in animals and in man, polyuria is an evidence of slight or early disturbance of the kidney vessels, whereas oliguria represents a much more severe type of functional damage. The polyuria of vascular irritability will result in the excretion of a urine having low specific gravity and low sodium chloride concentration, even when the ability of the kidney to excrete salt is not itself disturbed, as determined by the response to added sodium chloride, as well as by the high concentration in portions of the daily urine. They name this "vascular hypostenuria," and it must be sharply differentiated from the hypostenuria due to primary disturbance in the ability to excrete sodium chloride. This discrimination is of real importance in the management of clinical nephritis.

Closely allied to this state of irritability of the vessels is their susceptibility to fatigue. Schlayer, in his paper before the Kongress für innere Medizin in 1912⁴, demonstrated how the excessive use of a common diuretic of our daily food, ordinary salt, which always leads to increased output of water in the normal kidney, in the diseased kidney may produce rapid diminution of diuresis. A sharp restriction in the salt intake may then be followed by increasing outputs, both of water and salt. He made similar observations with the purin diuretics. Mosenthal and Schlayer (personal communication) have subsequently studied this in detail in experimental toxic nephritis. Their results, which will appear shortly, make it clear that abnormal susceptibility to fatigue is highly characteristic of the vascular system of the diseased kidney. This fact, like

⁴ Schlayer, Ueber die Ermüdbarkeit der Nierenfunktion, xxix Kongress f. inn. Med., 1912.





Diuresis of four days' duration from a single dose of caffeine, gr. 1, in a patient with chronic nephritis and myocardial insufficiency. The solid black columns represent the intake of water, and the hatched columns the output of urine, each in c. c. for each 24 hours.

the allied phenomenon of vascular over-irritability, must never be neglected in treatment. It justifies the already established custom of Romberg's Tübingen clinic, where the caffein diuretics were never given continuously, but intermittently, and in comparatively small doses. Our practical experience with these drugs at the Presbyterian Hospital bears out Schlayer's thesis. It is sometimes possible to obtain diuresis persisting for forty-eight hours or more from so small a dose as a single grain of caffein. When a diuretic of this type is indicated, as a rule we use theocin, giving three doses of 3 grains each for a single day, and not repeating until the diuresis resulting therefrom has ceased. Failure to respond to these diuretics should always indicate the need for at first diminishing, rather than increasing, the dose. The initial dosage of these drugs should always be small, because of the possibility of constriction resulting, rather than the desired dilatation. The response of the kidney vessels to digitalis seems to follow somewhat the same laws. Gottlieb and Magnus,⁵ Jonescu and Loewi,⁵ Kasztan⁵ and Fahrenkamp⁵ have shown definite selective action for the digitalis bodies, the arterioles of the kidney being dilated, while those of the intestine are constricted by small doses. Increase in the dose leads to general vasoconstriction, in which the kidney shares. Hedinger⁶ has published some experiments which seem to indicate a diuretic effect from digitalis in human nephritis without the least associated cardiac insufficiency. He is inclined to view this as evidence of increased susceptibility of the kidney arterioles, similar to their over-response to water, salt, and the purin drugs. Digitalis then becomes a possible pure renal diuretic.

While perhaps wholly speculative as yet, it is of interest to recall the fact that, following the lead of Jores and of Aschoff, there has been a general return by pathologists to the old view of Gull and Sutton that the primary contracted kidney, that type of kidney

⁵ Gottlieb, R. and Magnus, R., Ueber die Gefässwirkung der Körper der Digitalisgruppe, *Arch. f. exp. Path. u. Pharm.*, 1902, xlvii, 135; Jonescu, D. and Loewi, O., Ueber eine spezifische Nierenwirkung der Digitaliskörper, *Arch. f. exp. Path. u. Pharm.*, 1908, lxix, 71; Kasztan, Max, Beiträge zur Kenntnis der Gefässwirkung des Strophanthins, *Arch. f. exp. Path. u. Pharm.*, 1910, lxiii, 405; Fahrenkamp, Carl, Ueber die verschiedene Beeinflussung der Gefäßgebiete durch Digitoxin, *Arch. f. exp. Pathol. u. Pharm.*, 1911, lxv, 367.

⁶ Hedinger, Max, Experimentelle Studien über die Wirkungsweise von Nieren- und Herzmitteln auf kranke Nieren, *Kongr. f. inn. Med.*, 1910, xxvii, 750.

disease in which vascular irritability and the tendency to polyuria are most marked, is primarily a disease of the arterioles; that this disease of the arterioles is by no means limited to the kidney, but is widespread, the kidney participating in it now to a greater, now to a lesser extent. There is a tendency, which I have already discussed elsewhere, to consider the most characteristic symptom of this general arteriolar disease, high blood pressure, as associated with or dependent upon abnormal irritability of the diseased arterioles generally and especially in the splanchnic circulation. Inasmuch as such a drug as digitalis will produce dilation of the kidney vessels and constriction of the remaining splanchnic vessels, it seems not impossible that polyuria and hypertension are in their fundamental pathogenesis identical; that both are exaggerations of the normal vascular response in the organs concerned, under the influence of a disease whose functional expression is vascular over-irritability and whose anatomical expression is the arteriolar lesion described by Jores.

In the treatment of chronic nephritis of this type, von Noorden has always insisted upon the danger of abusing water. He urged this precaution in order to safeguard the heart from the bad effects of overfilling the blood vessels. Schlayer's work at least suggests that the constant overstimulation of the kidney by so apparently harmless a diuretic as water may entail danger to the integrity of its local vascular functions.

The overuse of salt clearly falls into this category⁷ and the French observers have insisted on the reality of increase in blood pressure and in uraemic symptoms from this cause, with corresponding improvement on a salt-poor regimen. In a number of cases I have convinced myself that, even in non-œdematous patients, restriction of the salt intake was one factor in the lowering of the blood pressure brought about by hospital treatment. In such patients, however, I have seen oliguria result from too protracted salt starvation.

In these vascular types of nephritis, caution in the use of the common beverages, coffee and tea, is likewise suggested. Hedinger⁸ has advised testing out individual nephritics with reference to their

⁷ See Widal and Javal, p. 41, *La Cure de Déchloruration*, Paris, 1906, J. B. Baillière et fils.

⁸ Hedinger, Max, *Ueber die Tagesschwankungen der Diurese bei gesunden und kranken Nieren*, Deutsch. Kong. f. inn. Med., 1912, p. 504.

functional response to the various diuretic substances contained in ordinary diets. He uses kidney tests meals and collects the urine at two-hour intervals throughout the test day. The observation of water output, specific gravity, the total output of sodium chloride and its percentage concentration, with comparison of the day and the night urines, gave interesting differences in the cases he studied. Normal persons responded in a typical way to the diuretic influence of the meal. Some patients with nephritis evidenced a striking over-response, while others of an advanced grade did not respond at all. The latter patients showed nocturnal polyuria. This method seems especially fitted to guide us in the intelligent dietetic treatment of patients with chronic nephritis.

Von Monakow⁹ has studied the response to water by means of a water test day, on which the patient took double the quantity of water contained in the regular diet. Such water tests are most important guides to treatment, especially in the convalescent stage of acute nephritis, but it scarcely seems necessary to make them very schematic, provided the intake and output are always definitely known. I should like here to call attention to the necessity for absolute uniformity in the salt intake when testing the excretion of water, and similarly the need for careful study of the relation between water and sodium chloride in making salt tests.

The study of the excretion of nitrogenous substances has also been carried on by von Monakow, who used urea in twenty gram doses added to a fixed diet, by Widal, who compared the blood urea with the protein intake, and by many others. The results in this field it is scarcely necessary to discuss from the therapeutic standpoint, apart from the obvious precaution of enforcing physiological economy of protein on general principles, as our means for combating nitrogen retention are conspicuous by their absence. I am convinced that the observation of the uncoagulable nitrogen of the blood, even by such simple methods as used by Widal in the estimation of the blood urea, is of great importance prognostically, but does not yet help us to make the outlook any less grave. In the same way, the sulphonaphthalein test, while of the greatest prognostic value, cannot serve in any way as a guide to treatment. In chronic passive congestion of the kidney, however, it may frequently afford a most useful measure of the degree of improvement

⁹ Beitrag zur Funktionsprüfung die Niere, Deutsch. Arch. f. klin. Med., 1911, cii, 248.

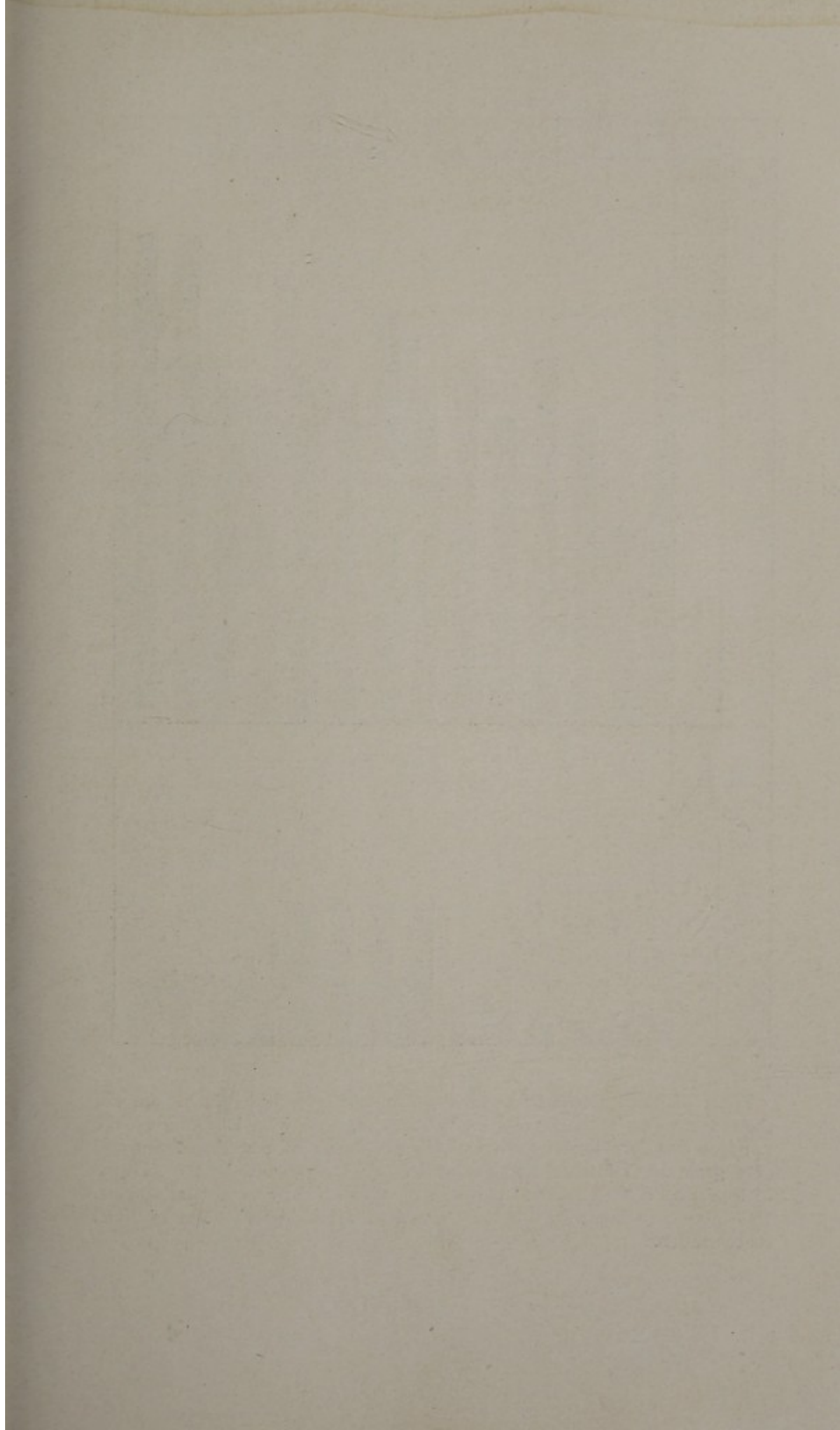
in kidney function during treatment. The same considerations hold good for Wohlgemuth's diastase tests.¹⁰ Geyelin's observations in my wards have shown, as a rule, a considerable parallelism between it and the phthalein output.

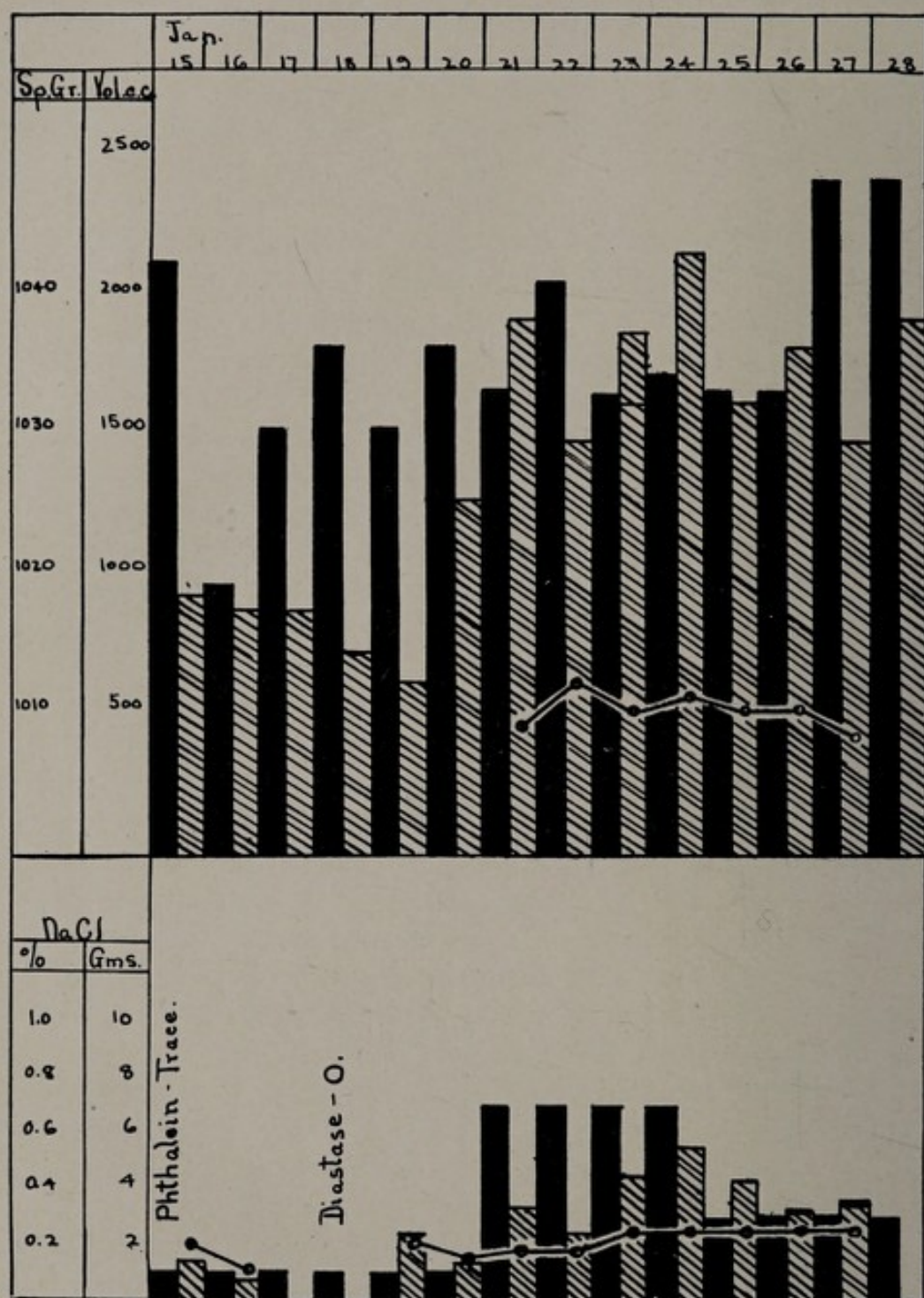
The treatment of œdema in nephritis is much more satisfactory. The functional studies which have resulted thus happily have been of a somewhat different order from the foregoing. The observations of Widal and of Achard, brought together in the admirable little monograph of Widal and Javal, *La Cure de Déchloruration*,¹¹ have put a simple and usually effective weapon against renal dropsy into the hands of every practitioner. The salt-poor diet is the result primarily of Widal's observations on the strict parallelism between ingested NaCl and body weight in a nephritic with obstinate œdema. By reducing the sodium chloride of the diet to one and one-half grams a day he was able to free his patient completely from œdema. On then adding salt, he brought about first a gain in weight without evident œdema; then, if the salt were continued, the reappearance of œdema, which in turn was promptly absorbed when the salt intake was again reduced to a minimum. Subsequently this method of "demineralization" was extended to the treatment of other types of œdema, sometimes with success, and to other forms of renal disturbance in which its rationale is not so clear. In the treatment of the oedematous types of subacute and chronic nephritis, however, it remains the most effective measure.

Schlayer and Takayasu's studies of salt excretion indicate that this occurs predominantly through the tubular epithelium. Von Monakow's studies of human nephritis confirm this. Extreme diminution of sodium chloride excretion may exist with slight damage to the other functions of the kidney, except the secretion of water. Among the test substances used, potassium iodide parallels the sodium chloride most closely, though in a review of 114 cases of renal and cardiac disease at the Presbyterian Hospital, in which we have followed various functional tests, a delayed potassium iodide excretion has occurred in non-œdematous cases of nephritis

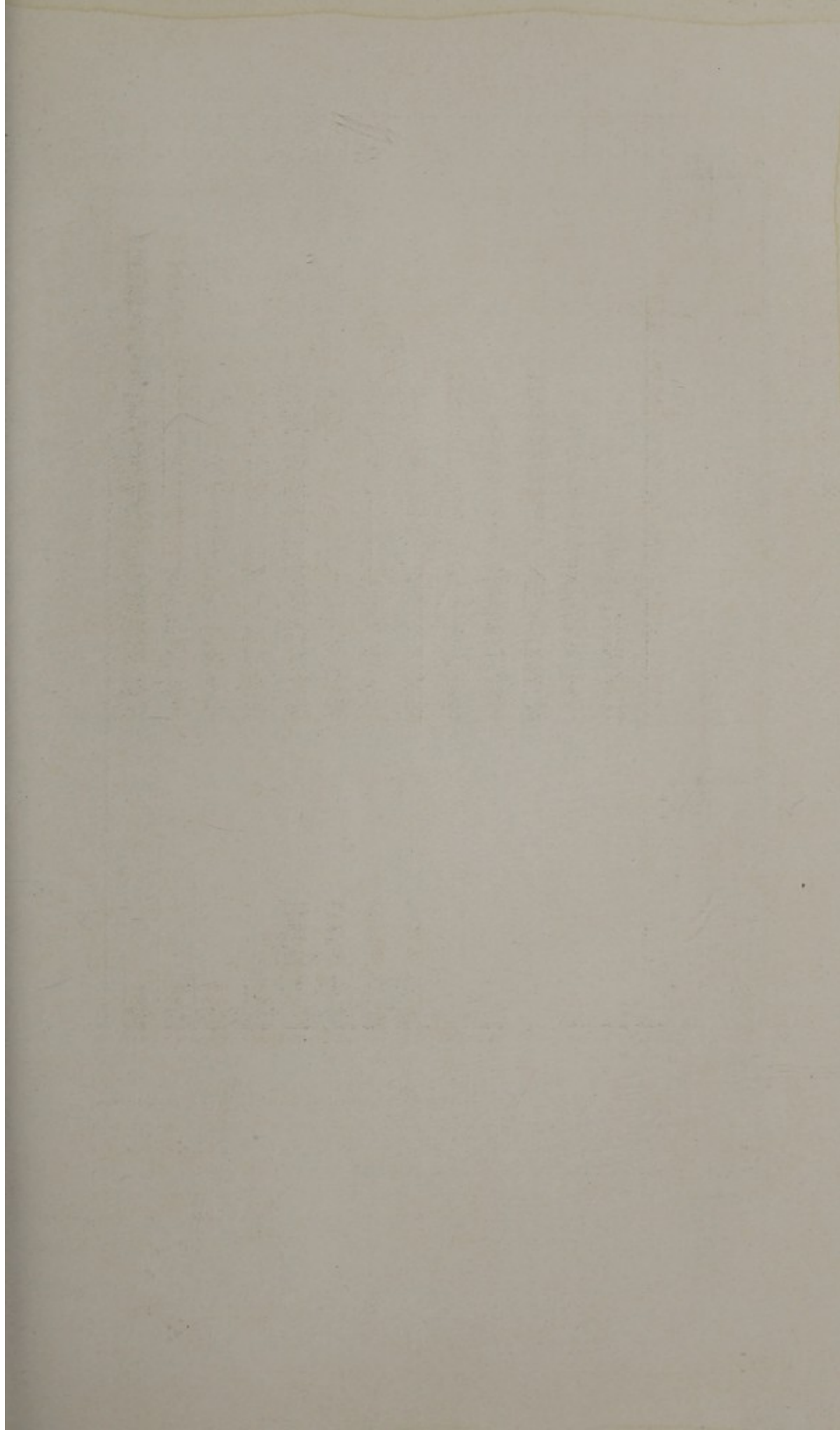
¹⁰ Wohlgemuth, Julius, *Experimentelle Untersuchungen über das Verhalten der Diastase im Blute*, Verhandl. d. xxv Kongr. f. inn. Med., Vienna, 1908, p. 500; *Untersuchungen über die Diastasen*, Biochemische Zeitschrift, 1908, ix, 10; *Experimentelle Beiträge zur Prüfung der Nierenfunktion*, Zeitschrift f. Urologie, 1911, v, 801.

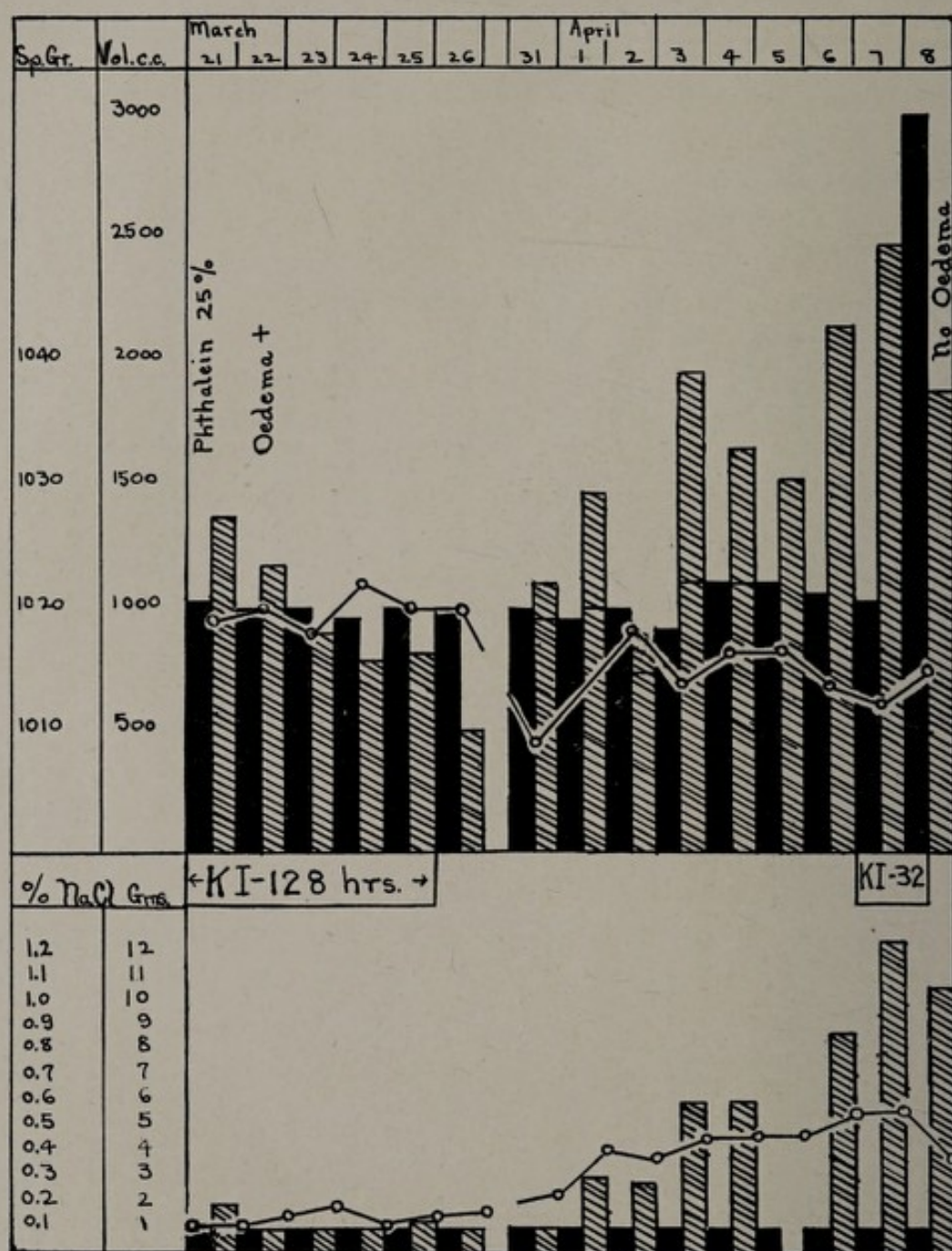
¹¹ Paris, 1906, J. B. Baillière et fils.





Effect of NaCl intake upon urine volume of a patient who at autopsy showed extreme atherosclerotic, contracted kidneys, who had continued a salt-free diet for himself for six weeks previous. Note during the period of 1 gram NaCl intakes, the marked oliguria transformed by the addition of 6 grams of NaCl daily to polyuria, by 4 grams daily to normal outputs. Note corresponding with this the fixation of specific gravity and of NaCl concentration.





Effect of salt-poor diet in subacute nephritis. Note the simultaneous increase in urine volume and both absolute and per cent. of NaCl excretion after absorption of oedema began, with return of greatly delayed potassium iodide excretion to normal. The curve on the upper portion of the chart gives the specific gravity, and on the lower the NaCl concentration in percentages.

with a normal total and percentage salt output. Schlager believes that the iodide excretion suffers earlier than the sodium chloride.

With the restoration of kidney function and the absorption of œdema, we have observed the return to normal of greatly delayed potassium iodide excretion. A most striking example of this was a patient with so-called chronic parenchymatous nephritis, who had had some swelling for eighteen months and marked oedema for two months. Her general anasarca was uninfluenced by salt-poor diet for five weeks. The salt outputs were below two grams a day, often below one gram. Extra water was not excreted, nor was any of an added ten grams of sodium chloride. Potassium iodide required 144 hours before its disappearance from the urine. With persistence in the salt-poor diet and hot packs, rapid absorption of the œdema followed. Sometimes as much as fifteen grams of sodium chloride were swept out in twenty-four hours, and the weight dropped forty-six pounds in thirty-one days. With this, the time required for the excretion of potassium iodide was reduced to seventy-two hours. The other functional tests were almost normal, the sulphonaphthalein excretion being forty-nine per cent at the worst. Now, one year after the patient's discharge, she remains absolutely free from any evidence of nephritis, either urinary or cardiovascular; an added ten grams of salt is excreted promptly, and the potassium iodide elimination is complete in less than forty-eight hours. I consider the potassium iodide test as giving an interesting side-light upon kidney function and its restoration in these cases, rather than as a guide to treatment.

What constitutes normal elimination time depends largely upon the test employed. Schlager, using the Sandow test, considers sixty hours normal. Von Monakow, who tests with starch paste and nitric acid, makes forty-four hours the upper limit. We have found the latter test much more satisfactory, and I believe that few normal individuals continue to excrete amounts of iodide recognizable by this test for more than thirty-six hours. Faint traces are sometimes detected for a surprising length of time by the Sandow test.

The one essential guide to treatment, as Widal's studies have shown, is the absolute salt balance. It is immaterial practically, though highly important theoretically, whether the cause of the salt retention be in the kidneys or in the general tissues. For the purposes of this discussion, therefore, I shall omit further mention

of the underlying problem of œdema or the reverse problem of salt retention without œdema.¹² Salt and water are retained, and the œdema is to a large extent dependent upon this fact. The graphic record of daily salt intake and output, with the weight curve, permits of exact knowledge concerning the degree of salt retention. The management of the salt intake in such cases of renal œdema is altogether analogous to the management of the carbohydrate intake in mild diabetics. As long as œdema persists, the salt of the diet should be kept at a minimum. After the absorption of œdema, the ability to excrete added salt should be tested occasionally, and the intake increased correspondingly as the excretory function is restored. By the exact estimation of sodium chloride tolerance and the adjustment of intake at a point below the ability of the kidney to excrete salt, chronic cases may be kept free from œdema and its attendant discomforts over long periods of time, even where functional recovery is not complete.

At the same time, the management of the water balance demands equal attention. This is of special importance in acute nephritis, as von Noorden has shown. Intelligent care is possible only with the use of graphic records of water and of salt intakes and outputs. The best charts, I believe, are such as Schlayer uses, with columns in different colors. The relation between intake and output for both substances is far more important than the absolute amounts. Not the least contribution which the study of renal function has made to the treatment of nephritis is its method of visualizing the actual response of the kidney to our therapeutic measures from day to day.

¹² Ambard and Beaujard, *La rétention chlorurée sèche*, *Semaine medicale*, 1905, xxv, 133; Heineke, A. and Meyerstein, W., *Experimentelle Untersuchungen über den Hydrops bei Nierenkrankheiten*, *Deutsch. Arch. f. klin. Med.*, 1907, xc, 101; Schlayer, *Experimentelle Untersuchungen über nephritisches Oedem*, *Verhandl. d. xxiv Kongr. f. inn. Med.*, Wiesbaden, 1907; Schmid and Schlayer, *Ueber nephritisches Oedem*, *Deutsch. Arch. f. klin. Med.*, 1911, civ, 44; Pearce, Richard M., *The Production of Oedema*, *Arch. Int. Med.*, 1909, iii, 422; Fischer, Martin H., *Oedema*, 1910, John Wiley & Sons, New York.

ON THE STUDY OF RENAL FUNCTION: THE PROGNOSTIC VALUE OF STUDIES OF RENAL FUNCTION.

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Despite the increased light shed upon medicine generally by science, the aphorism of Hippocrates holds true to-day, "Experience is fallacious and judgment difficult." Constant daily contact with nephritis in ward rounds, interspersed with occasional visits to the pathologist, serves to convert such an opinion into a conviction. Even the best clinical training and experience do not fully equip the physician to cope successfully and authoritatively with the problem of prognosis in certain cases of nephritis, nor do they reveal the exact status of his patient in many other pathological conditions of the kidney. To his assistance then are lately brought renal functional tests.

The ultimate object of any line of work is often furthered by a temporary abandonment of the consideration of details concerned in its various phases, and the replacement of this by reflection upon it in its entirety and in its relationship to its environment. A comprehensive review of any field of research, particularly in regard to its relationship to the fundamental sciences involved and in regard to the absolute advancement resulting from it, is seldom amiss, since it often results in the disclosure of the uselessness and limitation of certain procedures, suggests new and better methods of attack and establishes within us a truer conception of the purport and importance of the work.

The development and introduction of numerous renal functional tests are in accord with the general trend of medicine of to-day. The importance of knowing the ability of any organ to carry on its work rather than the appearance of the cells engaged in the work is being ever more emphasized.

Determination of renal function is of vital interest alike to the internist and surgeon from the standpoint of diagnosis, prognosis

and treatment. The widespread nature of the importance of such determinations is probably not so apparent to those confining their attention purely to its medical or surgical aspect, but to those interested in methods of determining renal functional capacity as such it becomes firmly impressed as investigations are made in relation to acute and chronic nephritis, orthostatic or other albuminurias, arteriosclerosis, uremia, myocardial insufficiency, polycystic kidneys, obstruction in the lower urinary tract, cystitis, pyelitis, uni- and bilateral hydronephrosis, pyonephrosis, pyelonephritis and ureteral renal calculi, hypernephromata, renal tuberculosis and the numerous allied conditions calling for differential diagnoses.

The clinical diagnosis made, in any individual case before offering a prognosis, certain problems must be investigated. (1) What pathological condition underlies the clinical picture? (2) Is the condition localized to the kidney or is any other system (cardio-vascular) involved or likely to be involved? (3) What is the functional capacity of the kidney? Is this permanent or temporary, subject to change? (4) Is or is not the condition one amenable to treatment? Only by attention to all these factors can anything approaching correct prognoses be attained.

Renal functional capacity is usually ascertained in one of two ways: First, tests of excretory capacity through the quantitative determinations of the excretion of various substances in the urine, dyes—methylene blue, indigo, carmine rosaniline, sulphonaphthalein, other chemicals—potassium iodide, lactose, salicylates, sodium chloride, urea, sugar following phloridzin and the enzyme diastase. Second, tests of the retention through quantitative determination of the concentration of certain substances in the blood, ions through electrical conductivity, molecules through cryoscopy, urea, incoagulable nitrogen and cholesterolin.

The recent work of Folin and Denis¹ indicates that the concentration of urea 0.5 gm. and of total incoagulable nitrogen 0.6 gm. per litre heretofore considered normal, must no longer be so considered, since in sixteen strictly normal individuals the highest non-proteid nitrogen which they found was 26 mg. and urea nitrogen 13 mg. per 100 gms. blood. Slight nitrogen retention* may appar-

* One would expect the urea and total incoagulable nitrogen in the blood to be approximately inversely proportional to the excretory efficiency of the kidney since this is the only channel of elimination (practically speaking) for the nitrogenous waste products.

ently occur in many diseases, but in our experience with a large number of cases using the older methods and also Marshall's² new urea method, we feel that no great prognostic significance is to be attached to concentrations of urea less than 0.55 gm. and incoagulable nitrogen 0.50 gm. per litre. Greater concentrations than this, together with a serum freezing point lower than -0.60 are of the greatest prognostic importance. Evidences of retention reaching this degree we refer to as cumulative phenomena.[†]

These tests all prove of value prognostically, but some much more so than others. Those of most importance in Group I are the dye substances, especially the phthalein, and of Group II cryoscopy, total incoagulable nitrogen and urea. The phthalein test is of prognostic value in all pathological conditions, whereas certain cases of severe nephritis even in uremia show no marked increase in incoagulable nitrogen or urea. So the presence of cumulative phenomena is of the greatest prognostic significance, while their absence is not.

Functional studies reveal only the excretory capacity of the kidney. By themselves they do not make the diagnosis or settle the prognosis. Just as routine blood examinations occasionally reveal an unsuspected leukemia, the routine use of functional tests brings latent kidney involvement to light. These tests should be used routinely in conjunction with other procedures to aid in diagnosis, prognosis and selection of lines of treatment. Their importance in different cases varies. It is possible that a series of ten or twelve different tests may add little or nothing to our knowledge of the condition after a careful clinical study, whereas after equally as careful a clinical study one test, verified, may change all of our ideas concerning the diagnosis, prognosis and treatment; as for instance, in one of our cases where a boy prior to functional studies was considered the subject of a diabetes insipidus with an excellent immediate prognosis, and after one phthalein test, was recognized as a case of advanced chronic interstitial nephritis verging on uremia, which was substantiated at autopsy within two weeks. Because of our inability to determine in advance in what cases the functional studies will be of value, *their routine employment* becomes of permanent importance.

[†] The urea concentration in the blood may be very high in pneumonia as shown by Herter.³ Throughout this article, in speaking of its prognostic value, we refer only to uncomplicated cases of renal or cardio-renal disease.

Clinical or functional studies alone are inadequate from the standpoint of prognosis. The application at any one time of one or a series of functional tests reveals only a limited amount of information, e.g. the excretory power of the kidney at that particular time. This, apart from other considerations, may be of no great prognostic significance. In order to become so the data from such studies must be considered in conjunction with a careful clinical study of the patient, and the underlying pathological processes responsible for the clinical and functional pictures must be recognized, identified and understood.

Aside from or in the absence of clinical studies, repeated functional estimations with the employment of the appropriate tests over a varying period of time will reveal the nature (stationary, progressive, retrogressive) and degree of renal involvement and so prove of prognostic value. But even repeated functional studies prove of greatest value when associated with careful clinical studies, for it has been definitely established that functional pictures carry very different significance in various pathological (clinical and experimental) associations. Diseases may be functionally identical, clinically and prognostically different and vice versa. To illustrate, a very low condition of function as indicated by a very low phthalein output, together with marked delay in the excretion of chlorides, iodide and lactose, may be encountered in experimental chromium nephroses or in marked passive congestion (experimental or clinical). This may be followed within a week by a practically normal renal function, owing to regenerative processes in the first instance, and to the reestablishing of cardiac compensation and better circulation in the second, whereas findings identical with those originally encountered, occurring in a case of chronic interstitial nephritis, indicate impending uremia and a very grave prognosis. Again, identically low functional capacity in cases of urinary retention, associated with pyelonephritis and hydronephrosis on the one hand, and in chronic nephritis on the other, do not have the same prognostic significance since the surgical condition is amenable to treatment, whereas no efficient therapy is at hand in chronic nephritis. From this, the necessity of understanding the absolute significance to be attached to the findings of any functional test becomes apparent. Lepine has objected to the employment of any one substance for the purpose of estimating functional capacity of the kidney on the ground that the kidney does not excrete all substances with the same

facility and that data obtained from a study of the excretion of one substance, therefore, cannot be applied to others. He believes that each substance has its own coefficient of excretion. That there is not accurate and exact parallelism of excretion of all substances by the kidney, one is forced to admit, but that there does exist a certain degree of parallelism, the same general tendency of excretion for all of the substances so far used, is unquestionably true. The difference is of one degree. Familiarity with the meaning of these variations in degree to which peculiar prognostic significance attaches is most desirable therefore.

The value of any of these excretory tests is purely empiric because of lack of sound physiological information dealing with the ultimate physics and chemistry of the excretion of any substance by any part of the kidney—tubules or glomeruli. Experience has taught us that the failure of phthalein to appear in the urine, or its excretion in mere traces in the course of chronic nephritis, indicates impending uremia and grave prognosis, even in the absence of any definite knowledge concerning the excretion of any other substance. In other words, failure to excrete phthalein empirically signifies incapacity on the part of the kidney to carry on its work—hence a bad prognosis. But this does not hold for all substances. Failure to detect diastase in urine by the customary technique employed means renal injury, possibly severe renal injury, but not necessarily so.

How can we utilize functional tests to the greatest advantage prognostically? (1) The prognostic value of functional studies must be considered from two points of view: (a) As to the immediate outcome (days, weeks or months are here concerned); (b) As to the ultimate fate of the patient and the future course of the pathological processes. At present their value from the first point of view is definitely established and is here discussed in its various phases. Prognostic significance other than immediate will be revealed only in the course of years. In association with Dr. Thayer and Dr. Baetjer, an attempt is being made to learn of the condition, through correspondence and re-examination where possible, of all of our patients previously studied. Data sufficient for conclusions are not yet at hand. Surgically, little prognostic value other than immediate can be considered, since surgical interference so radically changes the conditions. (2) We need a much greater familiarity with the significance and reliability of the findings of all

these tests in all renal lesions, experimental and clinical, medical and surgical. (3) We must learn the relative ease with which each and every approved test responds to increasing degrees of injury of any type, such information as has been presented in experimental nephroses by Schlayer and his co-workers, Pierce, Hill and Eisenbrey⁴, Austin and Eisenbrey⁵, or in chronic passive congestion in more recent studies. (4) Experimentation and clinical experience must teach us upon which tests reliance as to prognosis can be placed in each and every type of renal disease. (5) We need a much deeper insight into the nature of the processes at work in certain diseases, e.g. eclampsia, kidney of pregnancy, certain types of nephritis, etc. We must learn whether certain symptoms, conditions and phenomena *are actually due* to the accumulation of toxins, ferments, etc., whether this accumulation does result from the failure on the part of the kidney to excrete them, or whether the kidney is the usual channel of their excretion. May not, for instance, certain of these phenomena be the expression of deprivation of the body of certain substances through excessive excretion through hyperpermeability? More light is needed on the factors responsible for hypertension, œdema, uremia, etc. *We must learn to recognize in what conditions the excretory power of the kidney is a real criterion to the patient's actual condition.* Prognostically, their value will thus be enhanced through a knowledge of the limitations of these tests. (6) Functional tests will become more generally used and hence of more value when we know which ones can be discarded without loss, and which combination of tests (the smaller, the better) will yield all the information necessary in any given type of disease.

Value in Medical Cases.

Until very recently, little or no prognostic value has been attached to functional studies in medical cases, although their worth in this connection is fully as great as in the surgical. The introduction of new tests, notably the phthalein test, and improvements in the technique relating to the old ones, are largely responsible for the change in the attitude of the profession. The limitations of the value of such tests must be clearly recognized. In all forms of renal disease, a prognosis only so far as renal efficiency or inefficiency can be made through their use. Death may occur from innumerable other factors concerning which they give no information.

In *acute nephritis* the prognosis is largely dependent upon the etiology. When associated with specific fevers it becomes impossible to ascertain whether the patient is suffering from a toxemia due to non-excretion, or one due to a specific toxin of the fever. The capacity of the kidney to excrete can be readily determined, but this means but little, prognostically, on account of the rapidity with which marked changes in this respect occur. Clinically, we have seen cases with but 10 per cent. phthalein output for two hours, excrete 28 per cent. four days later, and the normal amount within two weeks. Experimentally, chromium animals with a zero output for two hours have returned to a normal excretion within ten days, while twenty-four hours later, more chromium having been given, the phthalein was again not excreted. It is evident, therefore, that frequent repetitions of tests are very essential to prognosis in acute nephritis. But when a patient exhibits, as one of ours did, no phthalein, no lactose, together with a high blood urea concentration, the case must be considered a grave one, though not hopeless. The immediate danger from the renal-inadequacy factor is at least determined.

The functionally mild nature of a *chronic nephritis* is readily recognized. Associated with the albumin and casts, a slight increase in blood pressure, palpable vessels (arteriosclerosis?) and slight cardiac hypertrophy, there may be encountered a somewhat delayed lactose and phthalein excretion, a normal total salt output with a vascular hyposthenuria, but no evidence of cumulative phenomena. In such a condition the immediate outlook is favorable, but tests should be applied intermittently to determine whether the condition is stationary or progressive, and the rate of progression. In prognoses caution should be observed on account of the possibility of acute exacerbations becoming superimposed on the chronic process. Aside from this, the case may develop gradually into an advanced nephritis with marked renal insufficiency exhibiting uremia, into a nephritis with a cardiac insufficiency or with a vascular accident (apoplexy).

Advanced nephritis is indicated always by decreased excretory capacity and usually by cumulative phenomena. Although, clinically, it is difficult often to determine the severity of the condition, this is readily obtained through functional studies. Perhaps the majority of cases of chronic interstitial nephritis are clinically latent, unrecognized until the occurrence of serious or even fatal

complications. Uremia, clinically, may appear to come out of a clear sky, whereas its unsuspected proximity can be readily recognized, and its occurrence can be easily predicted through functional studies. In chronic nephritis, failure on the part of the kidney to excrete phthalein or lactose, together with marked cumulative phenomena, indicates renal insufficiency impending uremia and calls for a grave prognosis.

Other cases with marked clinical nephritis, even with mild uremia, but with less marked functional involvement, may be more difficult for prognosis. Many factors must be considered. Will the heart dilate? Will an apoplexy occur? Will an acute attack be superimposed? But so long as the renal function remains fair, say 30 per cent. phthalein for two hours, with cumulative phenomena absent, and none of the above complications arise, death from renal-insufficiency uremia is not at all likely and an immediate favorable prognosis can be given. Care must be used in predicting more than this. The tests should be repeated in order to follow the course of the disease.

That a good or normal phthalein output is occasionally encountered in the presence of definite nephritis has been pointed out in our earlier publication. At the same time, the absence of hyperpermeability to phthalein in all our studies was commented upon. Pepper and Austin have lately called attention to a case of nephritis with marked albuminuria, cylindruria and oedema in which the phthalein and total incoagulable nitrogen were normal, while the chloride output after additional salt was somewhat delayed. The phthalein output in this case, 67 per cent. for one hour, strongly suggests hyperpermeability. Baetjer,[†] in our clinic, has encountered four cases during the winter which clinically and functionally resemble Pepper and Austin's case and in all of which hyperpermeability to phthalein and lactose was strongly suggested. This type of nephritis is not well understood. Since all of the patients studied are still living,* the nature and extent of the anatomical lesions are as yet undetermined and the value or significance of functional studies in relation to them is not clear.† Since the patients have

* Pepper and Austin's case was decapsulated but the condition has not improved (personal communication).

† It is possible that this increased permeability is not a passive condition but an active functional response to some unknown renal stimulant which differs essentially from an ordinary diuretic.

continued to live, the tests furnished correct information so far as immediate prognosis, at least, is concerned.

Cardio-Renal Cases.

All grades of nephritis and myocardial insufficiency may be associated, and only through the use of clinical and functional studies can the cases be properly interpreted. By the combined studies it is possible in any given case to determine the relative responsibility of the kidney and heart, from the clinical picture presented, and thereby to arrive at a better prognosis.

Experimentally, it has been shown that in moderate degrees of passive congestion the excretion of lactose, iodide and salt may be delayed, while the phthalein output remains normal. Where the congestion is more severe the phthalein is decreased, but returns to normal with the earliest signs of improvement of circulation. Strauss and Hohlweg found that incoagulable nitrogen and urea of the blood are increased in chronic passive congestion, but not so strikingly as in nephritis, findings which we are able to corroborate.* Low phthalein and the cumulative phenomena therefore bear great prognostic and diagnostic significance in this group of cases, since they are only encountered with rather advanced nephritis or with a very severe passive congestion calling for a grave prognosis.

Moderately advanced nephritis, associated with a moderately myocardial insufficiency, often exhibits a fair renal capacity, in which case the prognosis rests more on the response of the heart to treatment than on the nephritis. An increase in the phthalein output may be the first evidence of restoration of cardiac compensation and hence it indicates a favorable immediate prognosis. The absence of cumulative phenomena, together with a fair phthalein output in any clinically severe cardio-renal disease, points to the heart as the responsible factor.

A very low excretory capacity with marked increase in blood urea, or total rest-nitrogen, or a very low serum freezing point, indicates either that the kidneys chiefly must be considered etiologically, or that the heart is in an extremely precarious condition, in either case the prognosis being grave. With or without cumulative phenomena, a very low excretory capacity, persisting after clinical evidence of

* In pure chronic passive congestion we have never seen the rest-nitrogen higher than 0.630 gm. per litre.

cardiac improvement, indicates severe nephritis and an unfavorable prognosis.

Myocardial Insufficiency.

Marked renal insufficiency may result from pure chronic passive congestion. Very exceptionally, clinically and experimentally, the functional studies reveal a decrease in function equaling that seen in the most severe grades of nephritis. Since the congestion for this must be of a most extreme grade, death is imminent on account of the heart. As a rule in myocardial insufficiency, with a symptomatic and urinary picture identical with that seen in a moderately advanced nephritis alone, or in nephritis associated with a cardiac break, renal function as indicated by both excretory and retention tests is surprisingly good. When low renal function is followed by an increased phthalein output, the amount of increase gives a fair approximation of the extent of the cardiac improvement.

Polycystic Kidneys.

All conditions of renal function may be here encountered, and a prognosis can be based upon functional findings in this condition, just as in chronic interstitial nephritis. A case has been reported exhibiting a normal function, death resulting from an intercurrent disease, while a zero phthalein was found by Pepper and Austin in a case dying in uremia. A case now under observation, the diagnosis being confirmed by collargol skiagram, has a fair function only, 20 per cent. phthalein for two hours.

Surgical Cases.

Uremia, after operation, has been responsible for a large proportion of the mortality in renal surgical cases, so that any method capable of furnishing information as to the probability of the occurrence of such a condition is of great importance to the surgeon.

Emphasis upon one point is needed, viz., a *fair or a normal renal function must not be interpreted as meaning that uremia or anuria will absolutely not develop after operation*, or as meaning that the post-operative function will be the same as that before surgical interference. Many accidents may occur. The subject of a perfectly normal function may, after operation, develop anuria and die, although other things being equal, he is much less apt to do so than

a patient who, prior to operation, has a low renal capacity. The great value of these studies, surgically, lies in their ability to reveal those cases which are suitable and those which are unsuitable for operation as far as the kidneys are concerned. They can indicate that uremia is certain to occur following operation in a given case, that certain cases are hopeless, others poor, good or excellent surgical risks, but they offer no absolute security that the subject of a good surgical risk will not develop renal insufficiency.

The previous knowledge of the renal function is also of prognostic importance in the event of development of post-operative uremia, for the occurrence of this condition, in one who has been previously shown to have a continuously low function, means a grave prognosis, whereas, in one who has had a good renal function, recovery is more probable.

The tests are of value in two classes of cases: (1) those with retention of urine, renal injury following, due to obstruction in lower urinary tract with back pressure upon the kidney resulting in functional changes, in hydronephrosis, or in pyelonephritis, etc.; and (2) those with unilateral or bilateral renal disease.

Obstruction in Lower Urinary Tract.

As a result of obstruction in the lower urinary tract, pathological changes may occur in the ureter and kidneys, dilatation of the ureters, varying grades of hydronephrosis and, as a result of the long continued high pressure, atrophy of the parenchyma of the kidney. Not infrequently, infection occurs with the development of a pyelitis, a diffuse or localized pyelonephritis, or pyonephrosis. The occurrence of these complications is often difficult of recognition and is often overlooked, especially in the absence of symptoms of renal inadequacy. Cystitis and associated albuminuria and cylindruria are usually present, albumin and casts not contraindicating operation. The urinary output may be normal in many instances, also the urea output and total solids, and yet the patient be on the verge of renal failure. Disastrous results may be certain to follow any surgical intervention at this time, yet often nothing outside of functional studies can furnish this information.

A marked decrease in the excretory phenomena alone, or associated with cumulative phenomena, means severe derangement of renal function, which *may be of either a temporary or permanent*

character. No prognosis should be given and, except in emergency, or where the surgical procedure employed is the only method of improving or relieving the renal disturbance present, no surgical interference attempted without further study in conjunction with suitable preliminary treatment (Young's treatment—catheter drainage and abundance of water). Under this regimen repeated tests will quickly demonstrate the nature of the derangement, cases of nephritis and of true interstitial destruction showing no improvement, whereas purely functional changes or those secondary to pyelonephritis show markedly increased function.

This constitutes a very striking group of cases. A patient in uremia, with low excretory functional findings and with cumulative phenomena, may in the course of a few weeks return to an excellent clinical condition with a renal functional capacity approaching normal. Only one such experience is necessary in order to impress upon physician and surgeon the importance of determining (through time, preliminary treatment, and repetition of tests) the nature of the depressed function, temporary or permanent. The prognosis of the operation, so far as uremia and anuria are concerned, is infinitely better in those cases showing marked improvement in renal function following the adoption of the preliminary treatment above mentioned.

All tests are not of equal prognostic value in this group of cases. The phthalein has already established its place. Lactose is of no significance since its total suppression is frequently encountered when the phthalein, diastase, cryoscopy, blood nitrogen and urea, all show a fair or moderately good renal function, the truth of which is demonstrated in the subsequent history. In a series of 20 such cases lactose was recovered in the urine in only six instances. Glycosuria following phloridzin is also very slow in appearance or fails to appear at all. These two tests therefore exaggerate the degree of functional changes and bear no prognostic significance.

The phthalein test of permeability along with cryoscopy, urea and rest-nitrogen determinations of the blood give a sharp index of the functional capacity.

Unilateral and Bilateral Surgical Diseases.

The prognosis in unilateral and bilateral surgical diseases of the kidneys depends upon the surgeon's ability to recognize prior to nephrectomy which is the diseased kidney, or more diseased kidney, and what is the functional capacity of the kidney that is to be left to

carry on renal function, as well as upon his technical skill and the nature of the pathological condition present. Tuberculosis and pyogenic infections, unilateral and bilateral calculi, hydronephrosis, hypernephromata and congenitally deficient or non-developed kidneys are the conditions in which the test has proven of most value.

The urea, indigo carmine, methylene blue and diastase, cryoscopy, phloridzin, Alberran's polyuria test along with clinical studies and urinalysis of the separated urines will all indicate which is the diseased or more diseased kidney. But in this class of cases, the shortcomings of most of these tests are very evident, since one kidney may be doing two or three times as much work as the opposite one and yet be incapable of assuming the additional work or of carrying on adequate work unaided. It may be doing the major part of the work, but only at the expense of its reserve power. But phthalein has prognostically one great advantage over other functional tests, in that it indicates the absolute as well as the relative value of each kidney, so that one knows not only which is the diseased or more diseased kidney, but the amount of work each is doing relative to the other, and what is yet of greater importance, the amount of work for each relative to the normal, since this allows a prognosis concerning the capacity of the remaining kidney to carry on renal function. In double renal tuberculosis, in which, for instance, the amount of pus from each side is practically the same,* the phthalein test may demonstrate that one kidney has a function far in excess of the other, in fact so good a function that a successful nephrectomy can be done.

It must be admitted that depressed function, the result of inhibition due to ureteral catheterization, is sometimes encountered, in fact more frequently than we formerly believed. But in every case demanding ureteral catheterization, a total renal determination should also be made through which any discrepancy can be readily detected and error be thereby avoided.

Of prognostic significance also is the development of increased functional capacity in the remaining kidney after a nephrectomy. In those cases in which determination of function has been made after an interval of a month following operation, the capacity has not only been greater than that of the same kidney, but equal to, or

* Not infrequently in bilateral renal tuberculosis the more recently involved kidney secretes more pus than the other and only through functional tests can the true condition be recognized.

greater than that of the combined function of the two kidneys prior to surgical interference. The amount of increase function that will develop can of course not be predicted from functional studies, but the increase after nephrectomy can be determined from day to day and so aid in prognosis.

A perfectly normal urine in every respect except quantity may be excreted by a congenitally deficient type of kidney. Such a kidney may be capable of doing only one-fifth to one-tenth of the total work required. The literature furnishes numbers of instances of death following a nephrectomy, owing to the presence of this unrecognized deficient kidney, which has been left to do all the work. In the last four years of our experience, four such cases have been encountered, and in the last case only, the presence of a low phthalein from this kidney revealed its true nature and prevented the removal, on the opposite side, of a tuberculous kidney which had many times a greater function than this supposedly healthy kidney. Had the nephrectomy been performed, the prognosis would have been extremely grave.

In certain cases, owing to malformation or stricture in the lower end of the ureters, and especially in bladder tuberculosis, it may be possible only to catheterize one ureter. When infection of the bladder exists, microscopical and chemical examination of the urine collected transvesically is obviously unreliable as indicating a healthy or diseased condition of the uncatheterized side. It is therefore necessary to use functional tests to determine the presence or absence of disease and the extent of the disease where it does exist. A prognosis may be safely made concerning the ability of any kidney to carry on the renal function alone, even when catheterization of the ureter is impossible, and where the urine has been collected through a diseased infected bladder, provided a catheter can be inserted into the other ureter. The use of these tests should not be limited to renal surgery, since their routine employment would undoubtedly influence the surgeon's attitude in many instances.

Uremia. Uremia is a clinical condition, a syndrome, resulting from renal insufficiency from any cause. Its appearance is often sudden and unexpected, its course, acute and severe, rapidly ending in death, or chronic, lasting through months. Through functional studies it is possible to ascertain that it is impending, even when no indications whatever of its proximity are revealed by the clinical study. With a continued failure on the part of the kidney to excrete

phthalein and lactose, etc., association with the continuous marked and increasing accumulation of urea, or total incoagulable nitrogen, or low serum freezing point, one is perfectly safe in predicting the early appearance of uremia, regardless of the underlying pathological condition.

Uremia once present, the clinical severity is not a safe criterion for prognosis. Apparently desperate conditions sometimes reveal a fairly good renal function with an ultimate recovery, whereas very mild symptoms may be present until shortly before death. It always, however, indicates a serious condition, always calls for immediate therapeutic consideration and always suggests a grave prognosis, but it does not always indicate a hopeless one.

It has already been intimated that identical functional pictures carry very different prognostic significance in different clinical and pathological associations. Extremely low functional capacity in chronic nephritis means death, whereas in obstruction in the lower urinary tract with urinary retention and back pressure, the injury may be mostly functional, so that following appropriate treatment a fair or good capacity is again established. Nothing is more surprising than the rapidity and extent of the functional and clinical improvement. Whenever renal function markedly increases, surgical interference is much less liable to be followed by post-operative uremia, whereas in practically all cases with persistent low function it has followed operation used as a last resort, and death has ensued.

Markedly different clinical and functional conditions are encountered even in the medical uremia. Some cases of mild uremia, with nausea, vomiting and even stupor, show a phthalein output which is relatively high, 20-35 per cent. for two hours. This type is much more apt to be associated with cardiac or vascular changes, with oedema frequently a prominent feature. The uremia symptoms may here be an expression of a very different pathological condition than that encountered at other times, e. g., oedema of brain rather than a pure toxemia. These cases often improve and leave the hospital; if death supervenes, it is usually a cardiovascular affair and not a typical uremia.

Very occasionally with very low excretory function (traces of phthalein) and marked cumulative phenomena, the patient will continue to live in a chronic uremia for a surprisingly long time. In several instances such a patient has lived for some months, and in

one instance for as long as a year. This patient is in a desperate condition but still continues to live. Vicarious activity probably varies markedly in different individuals, and though incapable of carrying on life alone for any length of time, it probably is a material aid in the maintenance of life when the kidneys are just verging on inadequacy. The balance is not long maintained, however, and death is continually imminent.

Uremia cannot occur without valuable evidence appearing, as decreased excretory phenomena, but cumulative phenomena do not always arise. With Hohlweg we consider increased blood urea and rest-nitrogen indications of renal insufficiency and not of uremia.

The Prognostic Value of Each Test.

The employment of one test alone does not always yield all the information desirable. When only one is used, the phthalein test is undoubtedly the one of choice. Where it reveals decreased renal capacity, one of the blood tests, urea, total incoagulable nitrogen or cryoscopy, should be employed to determine the presence or absence of cumulative phenomena. These probably carry about the same significance.

Dye substances other than phthalein need not be employed prognostically, since they yield less quantitative and less reliable results and add nothing to prognosis.

The phthalein is the test for general use under all conditions. Its findings can be verified and its indications strengthened by the employment of selected tests in different conditions.

The iodide and salicylate tests are not of great prognostic value.

Lactose is unreliable, since its total suppression occurs in moderate lesion of a given type, but suppression in chronic nephritis indicates a severe lesion.

The urinary urea is of value only in relation to unilateral renal disease.

Phloridzin has a tendency to exaggerate the degree of functional injury and hence is not of great value.

Salt. A marked tubular hyposthenuria carries much prognostic significance, otherwise the chlorides are of only slight prognostic value.

Water. A very marked oliguria or anuria persisting is of significance.

Diastase may be tremendously depressed in moderate degrees of renal injury, while at other times it is not affected proportionate to the injury, hence it is not reliable for total capacity. In unilateral cases the diseased kidney is correctly indicated.

The value of total incoagulable nitrogen and of urea in the blood has been enhanced by the introduction of newer and more accurate methods by Folin and by Marshall. Increased concentration of these substances does not always occur in severe renal involvement, hence their normal concentration in the blood does not indicate normal kidneys. Their increase signifies renal injury, and the extent of the increase is of extreme value in determining the extent of the injury. They are not of value in determining the diseased kidney where only one is involved.

Cryoscopy occupies a similar position with about the same significance. A study of the combination of these three tests is needed in order to determine the extent of parallelism in their findings.

With cholesteremia we have no experience and with Ambard-Constant not sufficient to justify an opinion.

BIBLIOGRAPHY.

- ¹ Folin and Denis. Jour. Biolog. Chem., 1913, XIV, 29.
- ² Marshall. To appear in an early number of Jour. Biolog. Chem.
- ³ Herter. Johns Hopkins Hosp. Repts., 1900, IX, 96.
- ⁴ Pierce, Hill and Eisenbrey. Jour. Exper. Med., 1910, XII, 198.
- ⁵ Austin and Eisenbrey. Jour. Exper. Med., 1911, XIV, 366.
- ⁶ Pepper and Austin. Amer. Jour. Med. Sci., CXLV, 1913, 254.
- ⁷ Baetjer. To appear in an early number of Arch. Inter. Med.

For detailed consideration of various tests, see previous communications on functional studies by the author and his co-workers:

- Jour. Pharmacol. and Exper. Therap., 1910, I, 579.
- Ann. d. Mal. d. Org. Gen.-Urin., 1911, XXIX, 289 and 414.
- Trans. Amer. Assoc. Gen.-Urin. Surg., 1910, V, 59.
- Arch. Inter. Med., 1912, IX, 284; 1913, XI, 121 and 258.

DISCUSSION.

DR. HUGH CABOT (Boston): I believe that the choice of this subject of the Study of Renal Function for a general discussion this afternoon will be found to be an exceedingly happy one. There is no department of medicine, however wide or however narrow, in which we are not concerned with this question; and it is only of

recent years—and not even to-day sufficiently—that we have been realizing our responsibility with regard to knowing as practically, or as nearly as we can, the advances in the study of the kidney function.

The papers read here this afternoon have been of unusual value. Dr. Christian has brought to us his wide knowledge of the work of others, and his special knowledge, regarding the diagnosis of renal disease. Dr. Rowntree has come to us with uncalled-for modesty with a study of, I believe, the most valuable test from the point of view of prognosis, and has sketched for us its relation to the other tests in the field. Finally, we have had the view of the clinician, thoroughly equipped to use these tests, presented to us by Dr. Janeway.

We may look at the study of kidney function from two angles. First, there is the view of the clinical pathologist, who attempts to correlate the finding in the urine with those in the kidney; and it cannot be said that to him the tests of renal function have been, as yet, of great value. The other point of view, with which I have been particularly concerned, is the value of the study of kidney function with regard to prognosis. I, being essentially a bloody-minded person, am desirous of knowing whether or not I may, with more or less safety to the patient, operate in the presence of renal disease. It is, however, a fact that to-day too many surgeons neglect this matter of the study of kidney function, saying that the study of the urine will give them sufficient knowledge. It has already been pointed out that the ordinary routine examination of the urine will not give information on which the surgeon is at liberty to act; yet many go ahead, on the assumption that it will.

To come strictly to the point that I want to discuss, the value of these renal-function tests in enabling us to discover beforehand the probable mortality in any group of operations: The various tests have already been referred to, and I shall not go into them beyond saying that in my work I have come to rely on comparatively few of them. None of the color-tests, specifically so-called, seems as valuable as the phthalein test of Rowntree and Geraghty. We have used it in a very large number of cases and have come to regard it very highly. Another test that we rely on, which is of more confirmatory value than original value, is that of nitrogen retention. I am inclined to think of the work of Folin as bringing it much more nearly within the reach of the clinician. The surgeon may

depend on these two tests, if properly carried out, to give him a very good idea of the operative prognosis.

As a type instance of what I am considering, let us look at the cases, as they come to us, of obstruction of the lower urinary tract—a typical obstructing prostate. In a man in comparatively good condition, with only a moderate blood-pressure, with considerable residual, both without retention,—apparently a good risk,—we may find that the renal function, by phthalein and other tests, is reduced. We desire now to improve that function, institute methods of drainage, and it may appear that his condition is improving; but a careful study of renal function may show a steady fall in the amount of phthalein excreted and a very considerable nitrogen retention. This may be in advance of any clinical manifestations of trouble. Often the excretion of phthalein will fall from as great an output as 25 per cent. in the first hour after it appears, to unmeasurable traces; and not until it gets to the bottom of its fall will the patient show clinical symptoms. Then the excretion will begin to rise, and then the test, if all goes well, will begin to rise; but the patient will often improve more rapidly than does the test. If we operate on that patient, assuming that his condition is as good as it appears, in the face of a failing renal function, we shall kill him. If we operate during the rise, the prognosis is better; but we should wait until the rise has reached its crest, when the prognosis will be far better than when the patient first came under observation.

This type of condition in the kidney appears to me to be one not readily demonstrable, even by the pathologist. It depends on the acute congestion of the kidney and milder degrees of pyelonephritis, which do not produce a very permanent impression on the kidney, but reduces its functional capacity very rapidly and makes it a kidney from which we can ask little or nothing. Nevertheless, the power of the kidney to recover its function seems entirely good, and if we can give it a sufficient opportunity to do so, our prognosis will be of the best, and our mortality of the lowest.

Dr. Rowntree has already referred to the value of these tests of the severity of the disease in the two kidneys, so that one may be able to decide in advance of the operation whether the remaining kidney is of sufficient soundness to be compatible with life. That is a subject into which too little investigation is being made to-day in the general surgical world. I believe that it is possible at present

to determine with great accuracy whether the remaining kidney is sound enough to maintain life. That being determined, we have removed the largest factor in mortality.

Some attempt has been made to draw a line across kidney function, below which operation is dangerous, and above which it is safe. The more I see patients with impaired kidney function, the more I am impressed with the fact that no such line can be drawn. A kidney with low function may be incompatible with life in one patient, and quite compatible with it (but with very considerable added strain) in another. So far as I can make out at the present time, the most important thing is a stable kidney function. If the function is low, but is yet stable, and if the patient can be put to some strain without an important variation in the function's being produced, he is a far better risk than one with twice as good function, yet in whom the least strain produces bad results. Stability is more important than low level of kidney function. The latter does not necessarily contraindicate operation. Under these circumstances, if the level, although very low, is constant, we may advise operation and do it wisely under circumstances that make us willing to accept a very considerable risk; but we know what risk we are assuming, and do not give a comparatively favorable prognosis to a patient with a kidney whose function is such that the risk is rather grave or very grave, but is still one which we may properly take, if we realize what risk we are taking.

DR. GEORGE DOCK (St. Louis): Dr. Rowntree has given us an axiom from Hippocrates that is always worth while remembering in diagnostic matters. There is another axiom bearing on the matter of urinology, which is often used with more or less effect. Thomas Fuller, in his article on "The Good Physician," says: "The good physician trusteth not the single witness of the water if better testimony may be had. For reasons drawn from the urine alone are as brittle as the urinal. Sometimes the water runneth in such post haste through the sick man's body it can give no account of anything memorable in the passage, though the most judicious eye examine it," etc. This I have had written over the door in my urinologic laboratory for a long time; but, although the spirit of it is still applicable, I think we can say that the pessimistic sting of it has been materially taken away in the last few years.

I should like to reiterate Dr. Cabot's congratulations to this body for having heard the very comprehensive and clear and complete description of modern kidney-functional tests that we have had the opportunity to hear this afternoon. I cannot add anything to what Dr. Cabot has said; but it is noteworthy that we have had the statements from many who are actually doing the work that is necessary—the experimental work in the production of known kidney lesions; and also the clinical material, and then the careful clinical studies, including treatment, by Dr. Janeway.

Now urine-examination is very old, and a good deal of it is very good; but until recently it suffered, I think, from an unmistakable tendency that applies to all medical diagnosis: that is, the tendency to rely on a single diagnostic method and miss the complete examination of the sick man. For example, for a long time we depended on albumin tests. Too many patients were neglected or were allowed to be perfectly reckless on the basis of a single examination for albumin. The same thing was done with casts. We all remember how terribly the urea examination in urine was abused for years; and uric-acid examinations would have been much more abused, except for the fact that there were no easily applied methods of making them. When cryoscopy was put forth, many people looked on it as a complete relief from the other methods of time-consuming examination; take the freezing point of the urine, and you had the whole thing there.

It is a very interesting thing that the old methods of examination of the kidney function have been included in the papers and especially emphasized this afternoon by the speakers. The authors missed none of these well-known methods of examining the patient's condition. Physical examination, blood-pressure, and everything else were mentioned. Still more recently, however, there have been devised very exact methods of examining the blood, as elaborated by Folin and Marshall, and others. This advance can hardly be overestimated, and practically it means this: that in no clinic, no matter what kind of clinic it is, can these discoveries be neglected. I do not mean to say that they must be used blindly; but unless they are used as fully as their importance warrants in every individual case, then the patient will undoubtedly be a victim of malpractice.

Just how some of these examinations may be made, has often been stated. I shall not go into details; but in the last couple of years I had an opportunity of seeing at the hands of some of my

colleagues, and in my own clinic, some of the undoubted gains following the use of these methods. I shall mention only a single case that happened just before I left:

A man with the ordinary history came to the ophthalmological clinic on account of failing vision. He had albuminuric retinitis; and, although he seemed to have no indication of kidney disease, they sent him to the internal clinic to find out what was the matter with him. We found a typical condition, with slight enlargement of the left ventricle and high blood-pressure, but no history of serious interference with the kidney function. The urine was being passed in normal quantities. It had a specific gravity of 1012, and contained a trace of albumin and a few hyaline casts. It was, then, an ordinary case of contracted kidney; and the patient, in the ordinary course of events, would have had given him some advice about the diet and would have been told a few other things, and then sent home. I, however, applied, in the first place, the phthalein test, and found his excretion to be only 8 per cent. in three hours. We concluded that he was sicker than we had supposed. We put him to bed and treated him as well as most patients would have been treated under these conditions; although I should not like to claim that we did everything that was possible in the circumstances. Within twelve hours, he went suddenly into uremic convulsions, which it required a great deal of active work to modify. Even now, immense practical gains can be made from the application of these tests; but the most important thing consists in piling up evidence. Curiously, few cases that have been subjected to these newer methods have come to autopsy. The striking thing that comes out of Schlayer's communication (and a great many others have had the same experience) is that the patients on whom you make these tests do not ever seem to come to autopsy. I do not know whether or not they are treated better than they used to be, but there is a surprising lack of anatomical information. We need not only a much fuller knowledge of kidney function, because we are still ignorant of many details; but we need in the case of kidney disease an enormous amount of light on renal anatomy. The difference in the classifications and the many classifications of kidney diseases, as well as the hopeless difference of opinion regarding the classification of even the common kidney diseases, show how much we still have to learn. After we have applied the methods that we have and others that will, no doubt, be discovered, to the

study of the functions of the kidney during life, then complete anatomical information will give us an amount of exact knowledge for diagnostic and prognostic purposes such as we have never had at all in kidney diseases, and in very few other diseases.

I should like to suggest now, in regard to some of the anatomical work that has to be done, that it must be as complete and just as careful in all parts as the clinical work, in order to bring good results. We have long known that the anatomical structure in all parts of the kidney is not uniform; and the most minute and accurate studies must be made in all parts of the kidney in order to finally clear up the exact conditions in kidney diseases.

DR. JOHN T. GERAGHTY (Baltimore): The subject has been handled so thoroughly that I will make my remarks very brief, and limit myself entirely to the practicability of these tests and also the indications for their use.

The number of functional tests has become so great that it is impracticable to employ all of them in any individual case; and even, if not impracticable, nothing would be gained by employing all of these tests. The information furnished by many is of the same character, but more accurately furnished by one test than by others. For example, there is a parallelism between the excretion of the different dye substances; but, as phthalein furnishes more accurately all the information obtainable from this group of substances, no advantage attaches to the employment of all.

For chromocystoscopy alone, indigo-carmin is unquestionably the test of choice. Again, rest-nitrogen and blood-urea bear about the same significance.

Lately we have discarded the nonproteid nitrogen estimations, and are depending entirely upon the blood-urea (determined by Marshall's method), or upon cryoscopy, for evidence of cumulative phenomena.

From a practical standpoint, certain tests can be entirely discarded without loss; such as cryoscopy of the urine and electrical conductivity of the urine. Total urea estimations are of doubtful value, and diastase determination furnishes only information that is obtainable more accurately and quickly by other means. Certain other tests, such as potassium-iodide elimination, can be discarded as furnishing at times unreliable information. We have seen potassium-

iodide excretion delayed in cases with normal function (proven by subsequent history), and excreted within normal limits in cases of the most severe nephritis. The tests which we consider of the greatest value in the excretory group, based upon actual experience, are: phthalein, lactose, and chlorides; and of the tests of retention, blood-urea, rest-nitrogen and cryoscopy. The indications for the specific employment of the individual tests are as follows:

Chlorides, in all forms of nephritis and cardio-renal disease, especially if œdema is present; hyposthenuria being noted, together with its type.

Lactose is indicated for the detection of slight injury to the kidneys, and also in severe nephritis; since its suppression indicates a bad prognosis. It is not particularly helpful in surgical diseases.

Of the retention tests, either blood-urea, rest-nitrogen, or cryoscopy, is indicated whenever a severe lesion of the kidneys is suspected. We consider that one of these should be used as a routine, in conjunction with phthalein, wherever functional tests are desirable—particularly if the phthalein function is low.

Tests in conjunction with ureteral catheterization: In this connection, phthalein, urea and diastase are most serviceable. The diastase and urea give practically the same information, but only give relative functional values, while phenolsulphonephthalein gives both relative and absolute values. The total function should always be estimated by means of phthalein without ureteral catheterization, in order to detect the amount of catheter-inhibition, should this exist. Where severe bilateral lesions exist, one of the retention tests should be used.

Practicability of Tests. The simplest and easiest test is undoubtedly the phthalein test, as it requires the least amount of time and apparatus. The lactose test, if quantitative determination is required, necessitates the employment of an expensive polariscope. Furthermore, the preparation of the lactose for injection requires attention and consumes time. Its use also requires familiarity with the technique of intravenous injection.

Diastase requires the daily quantitative preparation of soluble starch, accurately graduated pipettes, and large series of test-tubes, a water-bath, and one-fiftieth normal iodine solution. For total estimation, it requires twenty-four hours specimens of urine with preservatives. The time necessary for a single determination is scarcely warranted by the information obtained.

Urea estimations of the urine can be accurately and rapidly done by the Marshall method; and, from the standpoint of practicability, it leaves little to be desired. It is useful only in conjunction with ureteral catheterization.

Chloride estimation, by the Lutke Martius method, requires standardized solutions, and carefully graduated apparatus. It consumes considerable time, and, besides, requires daily collection of the urine with a knowledge of daily chloride-intake.

All retention tests require, of course, the withdrawal of blood; and cryoscopy is, undoubtedly, the simplest, provided that proper apparatus is at hand. It requires careful attention to the details and consumes considerable time.

Blood-urea can be done by either the Folin or the Marshall method, and the total rest-nitrogen, preferably by Folin's method, but any of these methods is impracticable for the general practitioner.

Where only one test can be employed, the most value is unquestionably to be obtained from the use of phthalein; and this is particularly so from the standpoint of the surgeon. From practical experience with a number of the more promising tests, the information obtained is frequently unreliable. Phthalein alone has proved of value.

Estimation of function in renal surgery by means of phthalein has become so important that its position is firmly established. The surgeon to-day is not justified in performing a nephrectomy or other significant procedures tending to disturbed renal function, without having first learned the renal function.

Ureteral catheterization alone is not sufficient, with demonstration of apparently normal urine; as it not infrequently happens that the obviously diseased kidney is much the better kidney.

DR. WILLIAM S. THAYER (Baltimore): For the last two years, in association with Dr. Rowntree, Dr. Fitz and Dr. Baetjer, have studied the renal function of a considerable number of patients under my observation, in and outside the wards of the Johns Hopkins Hospital. These studies have taken into consideration the intake and the output of salt and water, the elimination of iodide of potassium and lactose after the manner of Schlayer, as well as the estimation of the incoagulable nitrogen in the blood and the excretion of phenolsulphonephthalein.

The delicacy of the lactose test, in the absence of chronic passive congestion, in revealing early disturbance of the vascular apparatus of the kidney, especially in association with the manifestation termed by Schlayer "vascular hyposthenuria" appears to be undoubted.

I can only emphasize, in my turn, the great importance, from all standpoints, of the systematic consideration of the intake and output of chlorides and water in renal disease.

The prognostic value of the estimation of the content of the blood in incoagulable nitrogen will probably be considerably enhanced through the recent introduction by Denis and Folin of simpler and more accurate methods of study.

All observations of the last three years have especially convinced us of the real diagnostic and prognostic value of the 'phthalein test of Rowntree and Geraghty. It is simple and easily carried out, and it appears to be a fairly reliable index of the renal function at the time of its application. The interesting parallelism between the 'phthalein excretion and the incoagulable nitrogen content in the blood, pointed out yesterday at the meeting of the American Society for Clinical Investigation, by Frothingham, will be remembered by those who were present. In Frothingham's experiments the increase in the incoagulable nitrogen appears a little later than the decrease in the 'phthalein output, but follows it very closely.

The elimination of 'phthalein is materially reduced in severe passive congestion of the kidney; it increases, however, immediately with periods of improvement, that which does not occur when sufficient damage has been done permanently to impair the renal function.

The detection of a low 'phthalein output, in some instances where there is no question of chronic passive congestion, may be of great importance from a diagnostic and prognostic standpoint. How important this may be, may be illustrated by referring again to a case mentioned by Dr. Rowntree: The patient was a boy, twelve years of age, who was admitted to the Johns Hopkins Hospital two and a half years ago, complaining of polydipsia and polyuria of several years' duration. For two years, the child had complained of pain in his legs, rather sharp in character and interfering with his walking. When he entered he was passing about 2,500 c.c. of urine in the twenty-four hours, of a specific gravity of about 1005, without albumen and without formed elements in the sediment.

The physical examination showed a pale boy with rather dry skin and with no demonstrable cardiac hypertrophy. His maximum blood pressure was ninety-five,—the radial arteries were, however, palpable, and thicker than one ordinarily sees in a small boy. The eye grounds showed no changes. The 'phthalein test, a week after entry, showed a total excretion in two hours of 7 per cent., and on the following day, the excretion was but 3.1 per cent. The test enabled us properly to interpret symptoms that we might well otherwise have regarded as those of diabetes insipidus. Within a day or two, the quantity of urine began to diminish, a trace of albumen appeared, and, inside of a week, the boy died in uraemic coma.

At the medical clinic of the Johns Hopkins University, we have already followed to autopsy probably fifty cases in which the 'phthalein test has been carefully made. In many instances, our ante-mortem opinion as to the extent of renal change, based upon the studies previously referred to, has been recorded. We are at present tabulating these cases, in the hope that conclusions of some value may be justified.

As Dr. Janeway has pointed out, we are concerned here in the main with chronic progressive disease, the ætiology of which is still, in many instances, uncertain, with conditions to combat which we have, at present, few weapons of decisive value. With what means we have now at our command, we have considerable power to *detect* renal disease. The most important immediate question which confronts us in many cases is as to the extent of the damage done and what is the outlook for the future. Let us not forget that these tests are tests of function and not tests of anatomical change. And, after all, that which is important for us to know is not so much what the kidney looks like, but how permanently are its functions impaired, and especially, what are the limits of its present powers, and how long may they be expected to last—when may we look for the onset of fatal decompensation? Here we must acknowledge still our serious limitations, for we can not invariably test the limits of functional capacity any more than we can test the exact limits of the compensatory power of the heart muscle. How far we can approach this has been brought out by Dr. Rowntree and by Dr. Christian. These are, however, questions of special importance in slow chronic nephritis.

When the excretion of lactose is suppressed, when the 'phthalein excretion is under 10 per cent. in two hours, where a previous per-

sistent vascular hyposthenuria has begun to disappear, where the urea content of the blood is high, the question is simple. But where the polyuria still persists, where the blood pressure is high, the lactose excretion delayed and the 'phthalein excretion moderately reduced, we are often asked: What is the outlook for life? How near are we to the danger line? These questions are not always easy to answer, for there are indications that occasionally decompensation may be sudden and unsuspected as it may be at times in disease of the heart muscle.

Nevertheless, such cases are exceptional, and I believe that to-day, thanks to the revival of the study of renal function, we are able to distinguish early disease of the kidney with greater accuracy, to estimate its extent more surely, and to prognosticate its future course more safely than we were a few years ago. More than this, as Dr. Janeway, especially, has pointed out, we have learned in some ways to treat our patients better, to improve materially their comfort, and to increase their chances of survival.

Of especial importance, it seems to me, from the therapeutic standpoint, are the observations of Mosenthal and Schlayer, which have been referred to by Dr. Janeway, emphasizing as they do and explaining the harm that may be done by undue persistence in the use of diuretics in renal disease. In every-day practice we have learned that the careless use of diuretics may be injurious, but the clear experimental demonstration of the reaction of the diseased or fatigued kidney to over-stimulation is a suggestive and helpful contribution.

DR. MOSENTHAL (New York): It is somewhat difficult to describe what occurred in these experiments, alluded to by Dr. Thayer, without adequate charts, but I will attempt to do so. In cases of human nephritis it is found that after repeated administration of diuretics the kidney not only frequently fails to react with diuresis to the later doses of the drugs, but that there may be a diminution of the amount of urine secreted. Such a fatigued condition, as it may be termed, is brought about by the diuretics given as drugs, caffeine, etc., as well as by those taken in in the food as salt, water, etc. As an example of the latter the cases of œdema due to primary salt retention, now treated according to the precepts of Widai and Strauss, are familiar to all.

It was determined to find out if experiment could throw any light upon this subject. Two poisons which produce nephritis were used: potassium chromate and uranium acetate. It soon developed that the damaged kidney could be fatigued in different ways. The condition of the kidney as determined by the form of poison injected, the number of doses of the diuretics as well as their strength, were all important factors in developing kidney fatigue. Using salt and caffeine as diuretics two distinct types of fatigue were developed, the one brought about by salt and broken through by caffeine, the other in which the reverse held true. It was always possible to predict that the rabbits poisoned with uranium held true to the former type, those with chromium to the latter.

Exhibiting such an extreme variation in function it is rather surprising that the histological picture of these two forms of nephritis is very much the same. Transferring these observations to human nephritis it is obvious that except in the instances of the "Widal" or "Strauss" cases referred to above we do not know which diuretics will be of value in producing a flow of urine. If the drugs are employed in too high dosage or too frequently, more harm may be done than good, the urinary secretion may be diminished or even completely suppressed. It is therefore necessary for the intelligent treatment of these cases to use the various diuretics in small doses and by comparing the twenty-four hourly output of fluid with the intake to note the exact effect that is being achieved and accordingly increase, diminish or change the medication used. It is the nearest approach we have towards furnishing a rational drug therapy at the present time.

DR. HENRY A. CHRISTIAN (Boston): I should like to emphasize further the damage that can be done to patients with nephritis by using diuretic drugs. All forms of diuretic drugs are capable of injuring patients with nephritis. That is a matter that we observed in our patients in the wards. It is a matter that we can demonstrate experimentally on animals.

Caffeine, diuretin, theocin, potassium acetate, etc., administered to animals which have severe nephritis, will materially shorten the lives of the animals. In other words, the injudicious use of any diuretic, far from being a benefit, may be distinctly injurious to the patient. Naturally, that is more definitely the case in patients with acute nephritis or chronic nephritis with acute exacerbations,

than in patients with chronic nephritis. It seems very probable that the functional study of the kidney is to give us a considerable insight into this question of the use of diuretics. Until we get more information on the subject, I am very certain that we shall do as we have done in the past: sometimes injure, and not benefit the patients, by using diuretics. I refer to the simple diuretics, and I refer to them as used in ordinary therapeutic doses, and not in very large doses. While we have shown in our experimental animals an actual increase in the anatomical lesion in the kidney, due to the use of these drugs, an anatomical lesion is not a very good measure of the disturbance in kidney function; but, when we have it, we can be certain that we have produced extensive functional disturbance. I should like to emphasize the point that we can do great damage by using diuretics injudiciously.

DR. THEODORE C. JANEWAY (New York): I welcome the opportunity to say, in closing, a word that I was unable to say in my part of the discussion. It is this: I should like to have it clearly understood that these functional kidney tests are divided strictly into two groups, and that they proceed to the solution of two wholly different problems. The test brought out by Dr. Rowntree is a test which aims at the solution of the old, pressing clinical problem, the prognosis, especially as a guide to surgical procedure. It is admirable and answers that need better than anything else that we possess to-day. From the medical standpoint the test is a rough quantitative measure of total kidney function—whatever that may be; I do not think we are in a position at the present time to say what is the total kidney function. It answers to the diagnostic need presented by patients with cerebral symptoms—whether due to focal vascular brain lesions, or to the toxic states which we call uræmia. I recall two interesting examples. One was a patient with high albuminuria, extreme headache, and the general picture of nephritis, who excreted phthalein. The headache persisted until the spinal fluid was drawn and it was found to be yellow tinged. She had had an old cerebral hemorrhage. The patient fell into a state of acute coma and died twelve hours later. At autopsy, a clot was found on the floor of one lateral ventricle, and the other ventricle was full of blood. The condition here is a widespread vascular disease, and sometimes the kidneys are spared remarkably. The phthalein test helps to clear up these

types. In addition I have seen liver disease with terminal coma discriminated by the phthalein finding of 70 to 80 per cent., and verified shortly by the autopsy. It has shown that chronic passive congestion is a real disease of the kidneys and not merely a functional sequel, the result of lesions elsewhere. The phthalein test shows us what the symptoms have always shown us, that it is a state dependent on anatomical lesions, well defined, and of practical importance.

The work of Schlayer, on the other hand, has proceeded from an entirely different standpoint, a fundamental one to medical men, but not of particular interest to the surgeon; that is the standpoint of the qualitative analysis of the disturbance in function within the kidney, which we must remember is both a compound and a complex organ. The individual kidney unit, the glomerulo-tubular structure, is highly complex. Up to the present time, normal physiology has not solved the problem of the correlation of function with anatomical differentiation of structure in the kidney unit. Until it does, we are in no position to demand of tests, in complicated pathological states, that they shall solve the same problem. What I think is going to come of this study of the physiology of the kidney is what resulted from the study of the physiology of the central nervous system. The careful study of the results in the focal lesions of the central nervous system and tract degenerations has made possible the greatest contribution to our knowledge of human physiology—cerebral localization. If we of the medical clinic coöperate with our colleagues, the pathologists in the autopsy room, and carry out over long periods of years the most exact functional tests of all kinds, at all times, not aiming at immediately practical results but at as clear an analysis of the functional disturbance as is possible; and in the end we are able in different institutions to bring together large groups of cases that have been studied for years, with the eventual histological findings in the kidney, we may do what the brain pathologists have done—add vastly to the understanding of the normal secretory activity of the kidney and its localization in essentially differentiated anatomical structures.

