[From the Transactions of the Congress of American Physicians and Surgeons, 1913, IX, pp. 23-53.]

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

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Read at the IXth Triennial Session of the Congress of American Physicians and Surgeons, Washington, May 6 and 7, 1913.

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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 (cardiovascular) 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, sulphonephthalein, 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 cholesterin.

The recent work of Folin and Denis[1] 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 nonproteid 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 nitrogeneous waste products.

ently occur in many diseases, but in our experience with a large number of cases using the older methods and also Marshall's[2] 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 —.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 reëstablishing 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 Eisenbrey[4], Austin and Eisenbrey[5], 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 toxines, 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 œdema 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,[7] 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 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. Tuberculous 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 œdema 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., œdema 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 lesions 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.

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[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 am I 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-carmine 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 indication 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 wherever 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, a 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 Widal 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.