

the use of local anesthesia which are exceedingly valuable, namely, in the first place, you are compelled to pay closer attention to your operation when the patient is awake than when he is asleep. It is not possible to sit and think while you are trying to make out what to do. Again you must do the operation, if it is performed under local anesthesia, with the least possible amount of traumatism. I believe that any surgeon who tends to be violent in his operative procedures should operate under local anesthesia, because the patient will not submit to a violent operation, and the surgeon will thus be prevented from doing harm. In my own clinic I have repeatedly operated under local anesthesia, but only rarely during the past four or five years, because experience has shown that this does not increase the safety. The method that I have found safe and satisfactory consists in giving the patient $\frac{1}{4}$ gr. morphin hypodermically, and 1/100 gr. atropin one-half hour before the anesthesia is given. The patient is then thoroughly anesthetized with ether by the drop method, placing the patient in a horizontal position until fully anesthetized and then elevating the head by placing the patient in the inverted Trendelenburg position at an angle of 45 degrees, causing an anemia of the brain, which lasts throughout the operation. The atropin prevents the accumulation of mucus in the larynx and that does away, virtually, with any possibility of pneumonia. So that these patients do not have pneumonia after the use of the anesthetic. The morphin prevents the sensitiveness and reduces the amount of anesthetic required.

The heart is improved by the use of ether. I have never yet seen a case in which the heart was not better after the anesthetic than before; and being under the influence of this morphin for half an hour before the anesthetic is begun, the patient goes under the anesthetic without the slightest excitement. Thus we make use of the principle which our distinguished President brought out some years ago.

Dr. JOHN ROGERS, New York: I wish to call attention to the comparative simplicity of these phenomena. They may all be referred to the thyroid alone or to the thyroid in connection with the associated glands. I must warn against operating on patients indiscriminately. Thyroidism can often be relieved by feeding substances not found in the thyroid. These preparations to which I have referred, which cannot be obtained commercially now, the Cornell Medical College will supply to you on request. There are many times when the use of the commercial thyroid is injurious; in fact, in the majority of cases it is injurious, on account of the chemical composition of the substance, as it does not contain all the normal ingredients of the gland.

In spite of what Dr. Ochsner has said, I must strongly advise against the use of ether. It is very easy under local anesthesia to make whatever division of vessels is necessary, or under nitrous oxid to remove whatever part of the thyroid you desire.

Dr. MARTIN B. TINKER, Ithaca, N. Y.: I have for many years championed the use of local anesthesia for this work and for much other surgery. A final decision as to its value may safely be left to those men who have had surgical experience, and who will take the trouble to see the work done properly under local anesthesia and compare it with the work done under general anesthesia. Not one, but many men have been converted to the use of local anesthesia in these cases after seeing it properly employed.

I have had experience in doing the work and seeing it done under both methods; not that I have had a great deal of personal experience with ether, but I had to give it in my early experience for others. If any of you see the relative simplicity of the local anesthesia method, the comfort and the safety of your patients, many of them desperate cases, and are not convinced, then I have nothing further to say.

Protozoa.—Verworn in 1888 made the statement that protozoa seem to have been especially adapted by nature for the purposes of the physiologist, for here, in the single cell, are performed all of the functions which higher animals perform.—Calkins in *Science*.

THE PHENOLSULPHONEPHTHALEIN TEST FOR ESTIMATING RENAL FUNCTION *

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INTRODUCTION

In July, 1910,¹ we presented our original communication on the results obtained on our experimental and clinical studies of the functional activity of the kidneys by means of phenolsulphonephthalein. Some additional data were presented in subsequent papers.² The present communication is a summary of our experience with the test during the past two years,³ and deals particularly with its value in relation to nephritis.

Phenolsulphonephthalein,⁴ which was first prepared by Remsen, is a bright red crystalline powder somewhat soluble in water and alcohol, but readily soluble in the presence of alkalis. The drug, as determined by Abel and Rowntree, is non-toxic, excreted with extraordinary rapidity, and appearing in the urine normally within a few minutes of injection. In alkaline solution a brilliant red color is produced, which is ideally adapted for quantitative colorimetric estimations.

TECHNIC

Twenty minutes to half an hour before administering the test, the patient is given 300 to 400 c.c. of water in order to insure free urinary secretion, otherwise delayed time of appearance may be due to lack of secretion.

Under aseptic precautions a catheter is introduced into the bladder, and the bladder completely emptied. Noting the time, 1 c.c. of a carefully prepared solution of the phenolsulphonephthalein containing 6 mg. to the cubic centimeter is accurately administered subcutaneously, intramuscularly or intravenously by means of an accurately graduated syringe. (We have used the Record 2 c.c. syringe, which is graduated in fifths of a cubic centimeter.)

The urine is allowed to drain into a test-tube in which has been placed a drop of 25 per cent. sodium hydroxid solution, and the time of the appearance of the first faint pinkish tinge is noted.

In patients without urinary obstruction, the catheter is withdrawn at the time of the appearance of the drug in the urine, and the patient is instructed to void into a receptacle at the end of one hour, and into a second receptacle at the end of the second hour.

A rough estimate of the time of appearance can be made by having the patient void urine at frequent intervals, without the use of the catheter. In prostate cases it is wise to have the catheter in place until the end of the observation.

When a catheter is to be employed, it is well to previously have the patient under the influence of hexamethylenamin.

Sufficient sodium hydroxid (25 per cent.) is added to make the urine decidedly alkaline in order to elicit the maximum color. The color displayed in the acid urine is yellow or orange, and this immediately gives place to a brilliant purple-red color when the solution becomes alkaline. This solution is now placed in a liter measuring-flask and distilled water added to make accurately 1

* From the Genito-Urinary and Medical Clinics of the Johns Hopkins Hospital and the Pharmacological Laboratory of the Johns Hopkins University. Read before the New York Academy of Medicine, May 4, 1911.

1. Rowntree and Geraghty: *Jour. Pharm. and Exper. Therap.*, July, 1910, 1, 570.

2. Rowntree and Geraghty: *Ann. d. mal. d. Org. genito-urin.*, 1911, 1, Nos. 4 and 5; Geraghty and Rowntree: *Tr. Assn. Am. Gen.-Urin. Surg.*, 1910, p. 50.

3. Detailed reports of our later studies will shortly appear.

4. *Ann. Chem. Jour.*, vi, 280.

liter. The solution is then thoroughly mixed, and a small filtered portion taken to compare with the standard which is used for all of these estimations.

Recently the Hellige hemoglobinometer, especially modified for use in connection with phthalein work, has been utilized. A standard alkaline solution, 6 gm. to a liter, is placed in the wedge-shaped cup. The urine collected is diluted to a liter and a small filtered portion poured into the rectangular cup. The wedge-shaped cup is now manipulated by means of the screw until the two sides of the color field are identical. The percentage on the scale is now noted. This instrument is much cheaper than the Duboseq and approximately accurate. Fairly accurate estimations, however, can be obtained by means of graduated cylinders—equal quantities of the standard solution and the diluted urine being used in separate cylinders, and the denser solution being diluted until the colors become identical. The amount of drug in the solution being known, the amount in the urine can be readily calculated.

When the collected urine has been made strongly alkaline, it is necessary to estimate the phthalein within a few hours, as the red color fades gradually under these conditions. When it is desirable or necessary to defer the estimation for some hours or days, it is better to make the urine distinctly acid, under which condition the phthalein remains unchanged. It should, of course, be made alkaline again when the estimation is made.

EXCRETION IN NORMAL INDIVIDUALS

The excretion has been studied in several hundred normal individuals. In our earlier work subcutaneous administration was used exclusively, the drug appearing in the urine in from five to eleven minutes, 38 to 60 per cent. (average 50 per cent.) being excreted in the first hour after its appearance in the urine, and 60 to 85 per cent. for two hours. In health the elimination is practically complete in two hours, only a trace being present during the third and fourth hours.

Recently intramuscular and intravenous injections have been employed. The time of appearance following the intramuscular administration is practically the same as that after the subcutaneous, but the output averages 5 to 10 per cent. more for the first hour. Following the intravenous injection, the drug normally appears in from three to five minutes, and from 35 to 45 per cent. of the drug is eliminated in the first fifteen minutes, 50 to 65 per cent. in the first half hour, and 63 to 80 per cent. during the first hour. This rapidity of the excretion, following intravenous administration, is exceedingly striking, and when this method is employed, observations for a quarter-hour or half-hour period only should be employed. For general use, however, we advocate the lumbar intramuscular method (the latter particularly when edema is present), as the technic involved is much simpler and the results obtained are reliable. The technic of the test is exceedingly simple. The injection is given, time of appearance noted, and collection of urine made for one or two hours. To each sample sufficient sodium hydrate is added to insure alkalinity and maximum intensity of color; then the urine is diluted to 1 liter, a small amount is filtered, the reading made, and the percentage of drug excreted is calculated.

INFLUENCE OF AMOUNT OF URINARY SECRETION

The excretion of the drug does not run parallel to the excretion of urine. It is immaterial as far as the excretion of the drug is concerned whether the urinary

output is 50, 200, 400 or 500 c.c. Similarly, the output does not seem to be much influenced by the previous administration of the different diuretics. Experimentally, on animals it was found that those diuretics (caffeine, urea, dextrose, phloridzin, calomel) which are thought to exert a stimulating influence on the cells of the renal tubules, slightly increase the phthalein output, whereas those diuretics (hypertonic sodium chlorid, potassium nitrate and digitalis) which act entirely by mechanical factors as by changes in osmotic tension, or changes in blood-pressure, slightly decrease or cause no change in the excretion of phthalein. No definite influence was noted in man, following the dosage usually employed for diuresis, one-hour estimations being made.

THE STUDY OF NEPHRITIS

Heretofore, functional tests have not been considered of any great value to the clinician in relation to nephritis. In fact, hyperpermeability to methylene blue, indigo-carmin and rosanilin has been shown to exist in acute and in chronic parenchymatous nephritis, while, on the other hand, decreased permeability with slow appearance and prolonged excretion has been demonstrated in the chronic interstitial variety.

ACUTE NEPHRITIS

An opportunity to study only five cases of acute nephritis has presented itself.

While no conclusions can be drawn from five cases, it is suggestive that in none of them was there increased permeability, but that, on the contrary, the permeability was markedly decreased when the condition was considered clinically grave.

CHRONIC PARENCHYMATOUS NEPHRITIS

In all, twenty-one cases belonging to the clinical type of parenchymatous nephritis have been studied. These cases represent different grades of severity and the duration of the disease varies from a few weeks to seven years.

In two very mild cases of short duration showing only slight edema, with albumin and casts, but with a normal urinary output, the time of appearance of the drug and the amount excreted was normal. In one of these cases the time of appearance was eight minutes and the output 52.5 per cent. for one hour. The second patient was a student who considered himself perfectly well, but in whose urine albumin and casts were discovered by chance. On close inspection, a slight edema about the eyes was detected. No other evidence or suggestion of the disease could be found. In this instance 53 per cent. for the first hour and 8.6 per cent. for the second hour was excreted following subcutaneous injection.

In cases of longer standing, or those in which the disease is of ordinary severity, the time of appearance has always been delayed slightly (ten to twenty-five minutes) and the amount excreted is definitely below normal.

In the most severe grades of chronic parenchymatous nephritis, or those in which the disease is of long standing and associated with secondary sclerotic changes, the output is reduced very markedly, and in some instances no trace of the drug can be found in the urine. Here, also as in the interstitial type, the absolute failure of excretion, or the excretion of a mere trace, has been followed within a short time by death from renal failure.

Although the number of cases of chronic parenchymatous nephritis has not been very large, sufficient data

have been collected to indicate that the test is of decided value in revealing the functional efficiency of the kidney in this condition. In the mild cases very little disturbance of function is indicated, and it may be impossible from the test alone to differentiate this condition from albuminuria. When there is a marked decrease in the phthalein output, marked renal changes are present, and when only excreted in traces, or not at all, a grave prognosis should be given, though no signs of uremia exist.

CHRONIC INTERSTITIAL NEPHRITIS

Twenty-two cases of the type clinically classed as chronic interstitial nephritis have been under observation. In many of these cases, previous to the administration of the phthalein test, no accurate idea of the degree of involvement of the renal function could be ascertained even after the most careful clinical study. The phthalein test has proved itself of immense value in revealing the degree of destruction of the renal substance, and has demonstrated itself to be of extreme importance from the standpoint of both diagnosis and prognosis.

In most of the cases of this series the time of appearance has been markedly delayed and the output of phthalein markedly decreased; where the output is lowest, the delay in appearance is most pronounced. The time of appearance, however, is not so important as the amount of excretion.

The following case is cited as an example of the accuracy of the test in revealing the true renal condition:

CASE 1.—Patient.—S. B. G., aged 55, surgical No. 25,174, was admitted Dec. 21, 1909, complaining of difficulty and frequent urination. These urinary symptoms were dependent on prostatic enlargement, the residual urine amounting to 440 c.c.

Examination.—Patient was apparently in good physical condition, well nourished, but slightly anemic. Urine slightly cloudy, acid, specific gravity 1.010, no sugar, slight trace of albumin and no casts. Urinary output 2,000 c.c. in twenty-four hours, urea ranging from 20 to 30 gm. for twenty-four hours. The phthalein test was given, a faint trace appearing in forty minutes, and at no time was more than the merest trace detected.

Repeated subsequent tests yielded always the same result. One week after administration the patient began to exhibit signs of uremia, which gradually increased until deep coma ended in death.

Autopsy.—Both kidneys presented marked atrophy, neither organ weighing one-third of normal, a severe grade of interstitial nephritis being present.

This case is of particular interest because of the fact that the urinary output, the urea, the total solids and the total nitrogen were normal and casts were also absent.

In the following case the diagnosis was exceedingly obscure until the evidence brought forward by the test was added. Before the administration of the test, nephritis was only one of many possibilities entertained.

CASE 2.—Patient.—Mrs. O., aged 47, admitted March 23, 1911, noted fatigue and dyspnea on slight exertion, together with slight edema of lower extremities. In December nausea and vomiting developed and have been present almost constantly since.

Examination.—The patient was poorly nourished and showed marked anemia; no edema of extremities. Urine was pale yellow, specific gravity 1.011, albumin, a trace; no casts on repeated examinations. Blood-pressure was 135. Eye-grounds were negative. Although nauseated, the patient was mentally bright and seemed in no immediate danger.

The phthalein test showed no output in three hours. Two days later the patient became irrational, dying within forty-eight hours in uremic convulsions. No autopsy was obtained.

The following case shows even more strikingly the ability of the phthalein test to reveal the presence of nephritis in the absence of any definite clinical evidence.

CASE 3.—Patient.—L. G., aged 12, admitted March 27, 1911, presented an interesting case of diabetes insipidus. The past history contained nothing of importance, except that large quantities of urine had been voided for some time and he experienced marked thirst.

Examination.—He was well nourished, not anemic, and apparently a normal-looking boy. His blood-pressure ranged from 80 to 90 m.m. Hg. Some thickening of the radial arteries was noted. No eye changes. The urine on admission was large in amount, 2,000 to 2,500 c.c., clear, specific gravity 1.005 to 1.010; no albumin, no casts. At this time no suspicion of nephritis was entertained. The phthalein test, performed March 28, showed an output of only 7 per cent. for two hours. Three days later only 2 per cent. was excreted. With the exception of the phthalein findings, absolutely no evidence of nephritis was present at this date. A week later the patient developed headache and a trace of albumin appeared in the urine. He rapidly became uremic and died April 9, 1911.

Autopsy.—A most intense grade of chronic interstitial nephritis was present, with almost complete disappearance of the cortex. A slight grade of acute nephritis was superimposed.

Chronic nephritis can exist over a long period without recognition, and may even exist in the absence of albumin and casts in the urine. The following is another case illustrating the presence of nephritis in the absence of positive clinical proof, and also the value of the phthalein test in revealing its existence.

CASE 4.—History.—F. G., aged 71, who had had six previous admissions for malaria, febricula, acute rheumatic fever and arthritis deformans during the last five years, was again admitted Nov. 7, 1910, for vertigo and attacks of loss of consciousness. Numerous urinalyses during these admissions failed to demonstrate any anomaly, except a trace of albumin at one single examination. An advanced arteriosclerosis and high blood-pressure were recorded on previous admissions.

Examination.—Urine was pale, 1.012, acid, albumin, occasional trace, no casts. Phthalein examination showed an output of only 5 per cent. for the first hour and 10 per cent. for the second, indicating a severe grade of nephritis.

Shortly afterward patient died of bronchopneumonia.

Autopsy.—Atrophy of the right kidney as the result of an old thrombosis of right renal artery, with chronic diffuse nephritis on the left side, small granular kidney.

UREMIA

In twenty-one cases under study, uremia has been present. Of this number, in fourteen uremia was grave; the patients exhibited nausea, vomiting, drowsiness or coma, and in several instances convulsions. In the remaining seven, mild symptoms only were present and had persisted over prolonged periods. Nine of the fourteen patients with grave uremia died during the attack. In all of these cases the phthalein elimination was zero or a faint trace only for two hours.

In two of the five patients recovering from their uremia, the output was 20 per cent., the uremia being the result of an acute exacerbation of a chronic nephritis. In two the output was 1-4 per cent.; in both of these the uremia was precipitated by a double pyelonephritis. The fifth case was one of acute exacerbation of chronic pyelonephritis in a man previously having had a nephrectomy. This last patient has greatly im-

proved, and at present has a two-hour excretion of 13 per cent.

In the seven mild cases, exhibiting slight but persisting symptoms of uremia, the excretion respectively was as follows: 10 per cent. in one, 7 per cent. in three cases, a trace in two, 2 per cent. in the other for two hours. Five of these patients died within three months of the performance of the test. Those living are still exhibiting evidences of chronic uremia, four months having intervened in one instance.

Of four patients not exhibiting uremia at the time of the test, but in which the phthalein output was below 8 per cent. for two hours, one excreting 6 per cent. died within two months, another within three months, and the other two are still living, in one two months, and in the other three weeks intervening, but both are exhibiting evidence of chronic uremia.

THE STUDY OF CARDIAC AND CARDIORENAL CASES

An attempt has been made to differentiate by means of this test between those cardiac cases with broken compensation or with passive congestion associated with the presence of albumin and casts in the urine and those cases in which cardiac insufficiency is associated with varying grades of true nephritis. In this connection thirty-three cases have been studied. From this study there appears to be no doubt but that decrease in function accompanies marked passive congestion of the kidneys in the absence of any true nephritis. As the cardiac condition improves, however, the passive congestion becoming less marked and edema subsiding, the output of phthalein increases, and in one case rose from 16 per cent. to normal in the course of one week, the patient in the meantime losing 70 pounds in weight with the disappearance of a general anasarca. We feel that the phthalein test will prove of value in determining what degree of renal efficiency exists in this class of disease, and subsequently with improvement in the cardiac condition and the disappearance of edema, a continued low phthalein excretion will indicate with considerable certainty the presence of permanent organic changes in the kidney. We feel, however, that a much larger series should be studied clinically and at autopsy before very definite conclusions can be drawn.

MISCELLANEOUS CASES

A large number of miscellaneous medical diseases have also been studied from the standpoint of phthalein excretion, among the number being ten cases of lobar pneumonia. In pneumonia the output is little if any decreased, and does not run parallel with the chlorid excretion. Three cases of persistent albuminuria have shown a normal output. In no disease other than renal, so far studied, has a marked reduction of the phthalein excretion been encountered.

THE RELATION OF PHTHALEIN OUTPUT TO BLOOD-PRESSURE, TO CHANGES IN THE EYE-GROUNDS AND TO THE BLOOD-PICTURE

In the majority of cases of chronic nephritis in which the blood-pressure has been high, the phthalein elimination has been markedly decreased, but no exact parallelism exists, inasmuch as not a few instances have been encountered in which the systolic pressure has been over 200 mm. Hg; and the phthalein output one-half of normal, while on the other hand there have been instances in which the blood-pressure has been normal while the phthalein output has been zero or nearly so, the patients shortly after dying in uremia. While a

high blood-pressure, when present, is considered of diagnostic and prognostic value taken in conjunction with other clinical data, yet many patients died of renal insufficiency and exhibited a blood-pressure which was normal or practically so. Nor is the blood-pressure, even when high, increased in inverse proportion to the decrease in renal function.

While in some instances marked changes in the eye-grounds, choked disk, tortuous vessels, hemorrhages, etc., have been present coincident with a very low phthalein output, in many cases, even of the most advanced and even fatal nephritis, no changes whatever in the eye-grounds could be detected, the patient at the same time failing to eliminate the phthalein.

Moderate or rather severe grades of secondary anemia in the absence of disease of the kidneys can be present without any diminution in the phthalein elimination; for instance, two patients, one with 2,500,000 red cells, and hemoglobin 30 per cent., the other with hemoglobin 30 per cent., eliminated 61 and 57 per cent. for two hours, respectively.

VALUE OF TEST FROM A SURGICAL STANDPOINT

Through the encouragement of Dr. Hugh H. Young we have been enabled to study the phthalein excretion in a large series of cases of urinary obstruction, in order to determine the value of the test in revealing the functional capacity of the kidney in these cases. This is a consideration of grave importance in this connection, since the development of uremia or renal failure has been responsible for a great part of the mortality following surgical interference.

As a result of obstruction in the lower urinary tract, pathologic changes may occur in the ureters and kidneys, dilatation of the ureters, varying grades of hydronephrosis, and as a result of the 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, particularly in the absence of symptoms of renal inadequacy. A large proportion of these cases of urinary obstruction have cystitis associated with albuminuria. The presence of casts in the urine is no contra-indication to operation. The urinary output may be normal, also the urea and total solids, and yet the patient may be on the verge of renal failure and disastrous results may follow surgical interference.

The test has been used in 100 cases of urinary obstruction, mostly cases of prostatic hypertrophy. The technic involved in these cases necessitates the use of a catheter, otherwise it does not differ from that described above.

In the majority of cases, the test indicates a more or less degree of renal impairment, and taken in conjunction with the clinical condition it is of more value than the study of urine output, total solids, total nitrogen, and urea estimations combined.

A marked decrease in the amount excreted invariably means severe derangement of renal function, which may be of either a temporary or permanent character. Under such conditions one should proceed with extreme caution, and no surgical intervention should be attempted without further study together with preliminary treatment. Under this regime, repeated functional tests will demonstrate eventually the nature of the derangement, for in true interstitial nephritis the output will continue low, whereas if the derangement is purely functional or secondary to pyelonephritis, usually improvement will

follow as a result of the treatment and will be indicated by a decrease in the time of appearance of the drug and simultaneously an increase in the amount eliminated.

The functional derangement due to infection in these cases is a much more dangerous condition than is the presence of even a fairly advanced condition of interstitial nephritis. The use of the test enables one to select the most favorable time for operation. In cases exhibiting a continued suspiciously low output, the use of nitrous oxid gas, or spinal anesthesia, is suggested as preferable to ether in order to protect the kidneys. When only a trace of the drug continues to be excreted, prostatectomy should not be attempted, even though the patient presents no evidence of uremia.

In our original paper we stated that a dropping phthalein output was a contra-indication to operation except in cases of necessity. This decrease in function usually means some change in the renal condition and in most of our cases it has been caused by the development of a pyelonephritis or an exacerbation of an old process. It is obviously wise to wait until the kidneys have recovered from this acute shock before subjecting them to further injury through operation.

The test can be used to equal advantage preliminary to any surgical procedure, when it is deemed important to know the true functional capacity of the kidneys.

TECHNIC OF THE PHTHALEIN TEST AS APPLIED TO ESTIMATION OF THE FUNCTION OF THE INDIVIDUAL KIDNEY

Functional tests have already demonstrated their value in this connection. But they have at most been able to determine only the relative working capacity of each kidney and have shed very little light on the absolute functional capacity of each organ.

The phthalein test in association with ureteral catheterization has been used in seventy cases of unilateral or bilateral disease.

Twenty minutes previous to examination 600 to 800 c.c. of water are given to the patient in order to insure a free flow of urine. The ureters are then catheterized.

As it is essential to collect all the urine secreted by each kidney during a definite period of time, in order to do accurate quantitative work, a form of ureteral catheter especially devised for this purpose has been used. The flute end catheter of Albarran, No. 6, or preferably No. 7, has been found to be most satisfactory. The catheters which have only side openings and no end opening cannot be depended on for this purpose.

The catheters are passed up into the ureters to a distance of four inches. The cystoscope is then withdrawn, leaving the ureteral catheters in position. A small ureteral catheter is now passed into the bladder and the bladder thoroughly emptied, so that leakage, should it occur, can be detected.

The time of injection is recorded, as is also the time of the appearance of the drug on each side. Starting from the time of appearance, the collection is then continued for one hour following subcutaneous or intramuscular injection. The amount of drug in each specimen is then estimated by the technic described above.

RESULTS OBTAINED WITH THE PHTHALEIN TEST

In normal cases the time of the appearance of the drug from the two sides has been almost always the same, and in the majority of cases this has been five to ten minutes following subcutaneous and three to five minutes following intravenous. The time, of course, will vary somewhat with the rate of urinary secretion. Nor-

mally the amount excreted by each kidney will be practically the same. The series of cases studied include tubercular or pyogenic infection, unilateral or bilateral, calculi, hydronephrosis, hypernephromata, etc.⁵

UNILATERAL OR BILATERAL SURGICAL DISEASE OF THE KIDNEY

It has been demonstrated that the time of appearance and the percentage of output is practically the same for the two healthy kidneys. When one kidney only is diseased, the time of the appearance of the drug is delayed on the diseased side, and the amount excreted is not only relatively but absolutely decreased. The amount of delay in the time of appearance is comparatively of little value. Reliance is only to be placed on the quantity excreted during a period of one-half or one hour, depending on the method of administration.

Although in the majority of these cases of unilateral disease the combined output is equal to that of two normal kidneys, the greater part of the excretion is shown to be performed by the healthy kidney. In proportion to the decrease in function on the diseased side, approximately there is a proportionate increase in the function on the healthy side. In such cases following nephrectomy the remaining kidney eliminates after the lapse of two or three weeks an amount of drug which is normally excreted by two healthy kidneys. In all cases studied, the output from the remaining kidney has been greater than the combined output from two kidneys prior to operation.

In bilateral disease it has been found possible to determine the individual function (absolute or relative) of each kidney. It is in this class of cases particularly that the shortcomings of other functional tests have been most apparent, as one kidney may be doing twice or three times the amount of work of the opposite kidney, and still be unable to assume the additional work of the other kidney. It may be doing the major part of the work at the expense of all, or nearly all, of its reserve power, but the phthalein test determines whether the kidney has a functional capacity which is normal, less than or greater than normal and to what degree. In three cases of double renal tuberculosis, in which the amount of pus from each side was practically the same, the test permitted it to be determined that one kidney in each instance had a function greatly in excess of the other, indeed sufficient functional capacity to allow of successful nephrectomy, marked improvement in general condition occurring subsequently in each case.

In six cases out of seventy we have found that the catheters caused some inhibition of function, as was also observed by Keyes Jr. and Stevens. This influence can readily be estimated by taking the total function either before or after catheterization.

The test has been used by us simultaneously with cryoscopy, phloridzin, indigo-carmin, and the polyurea test of Albarran. No particular advantage was added by combining with one or all.

CONCLUSIONS

1. The phenolsulphonephthalein as used by us has many advantages over all other functional tests thus far proposed.
2. Phenolsulphonephthalein itself is better adapted for use as a functional test than any other drug previously employed for the same purpose on account of its

⁵ The details concerning forty-two of these cases are considered in previous communications, *Tr. Am. Assn., G.-U. Surg.*, 1911, and *Ann. d. mal. d. org. génito-urina.*, February and March, 1911.

early appearance in the urine and the rapidity and completeness of its elimination by the kidney and the reliance to be placed on its findings.

3. The method of quantitative estimation of the amount of drug excreted is simple and exceedingly accurate.

4. It is of immense value from a diagnostic and prognostic standpoint in nephritis, inasmuch as it reveals the degree of functional derangement in nephritis whether of the acute or chronic variety.

5. In the cardiorenal cases the test may prove of value in determining to what degree renal insufficiency is responsible for the clinical picture presented.

6. The test has proved of value not only in diagnosing uremia from conditions simulating it, but has also successfully indicated that uremia was impending when no clinical evidence of its existence at the time was present.

7. The test has proved of great value in revealing the true renal condition in cases of urinary obstruction. It is here of more value than the urinary output of total solids, urea or total nitrogen and enables the surgeon to select a time for operation when the kidneys are in their most favorable functional condition. The improvement in the renal condition in cases of urinary obstruction, following the institution of preliminary drainage, is strikingly indicated by this test.

8. In unilateral and bilateral kidney disease the absolute amount of work done by each kidney, as well as the relative proportion, can be determined when the urines are obtained separately. We do not feel that this is always mathematically accurate, but in our series it has indicated the functional capacity to a degree not attained by any other test.

It is with the greatest pleasure that we thank Dr. Young for his early and continued interest in this work, and for the generous supply of clinical material referred to us by him, by Dr. Barker, Dr. Thayer and the other members of the hospital medical staff for the opportunity of studying the cardiac and nephritic cases, and Dr. F. W. Hobleman for his valuable assistance in carrying on the work, and Dr. Dunning of Hynson, Westcott, for kindly furnishing us with the phenol sulphonephthalein used throughout this study.

SOME OBJECTIONS TO THE USE OF ALUM BAKING-POWDER*

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NEW YORK

I. INTRODUCTION

During a period of about seven years I have occasionally conducted experiments on the effects of aluminum salts. These studies have convinced me that the use in food of alum or any other aluminum compound is a dangerous practice. That the aluminum ion is very toxic is well known. That "aluminized" food yields soluble aluminum compounds to gastric juice (and stomach contents) has been demonstrated. That such soluble aluminum is in part absorbed and carried to all parts of the body by the blood can no longer be doubted. That the organism can "tolerate" such treatment without suffering harmful consequences has not been shown. It is believed that the facts in this paper will give emphasis to my conviction that aluminum should be excluded from food.¹

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1. This paper is purposely restricted to a discussion of the work of the author and his collaborators.

II. EXPERIMENTS BY HOUSE AND GIES ON THE EFFECTS OF ALUMINUM COMPOUNDS ON THE GROWTH OF SEEDLINGS

Several years ago, in collaboration with House,¹ I published the general results of a study of the influence of aluminum compounds on typical seedlings. The essential facts in that connection were summarized in the appended statement and accompanying table (Table 1).²

Although aluminum compounds appear to exist in small proportions in many plants, and occur in traces in some animals, relatively little has been learned regarding the biological effects and significance of aluminum. The authors have begun a series of studies in this connection, the first of which has been an investigation of the influence of aluminum on lupin seedlings. The methods described by True and Gies³ were used, and the following compounds were taken: aluminum sulphate, aluminum nitrate, aluminum chlorid, aluminum-sodium chlorid, potassium alum, and ammonium alum. The accompanying table (1) presents some of the more significant results, which represent the average of very many observations for periods of forty-eight to seventy-two hours.

In nearly all cases, in these experiments, little or no effect was produced at a concentration of $m/65,536$ [i. e., per liter the molecular weight in grams divided by 65,536]. In concentrations greater than $m/65,536$, growth usually was markedly inhibited. In concentrations less than $m/65,536$ and down to $m/1,048,576$, or $m/2,097,152$, growth was stimulated as a rule.

TABLE 1.—DATA SHOWING THE COMPARATIVE EFFECTS OF ALUMINUM COMPOUNDS ON THE GROWTH OF LUPIN SEEDLINGS

Aluminum Compound	Greatest Molecular Concentration that Permitted Slight Initial Growth	Least Molecular Concentration in Which There Was No Growth After 24 Hours	Greatest Molecular Concentration in Which Growth Was Equal to that in the Pure Water Control	Molecular Concentration in Which Initial Stimulation Took Place	Molecular Concentration in Which the Maximum Stimulation Occurred
	m/x	m/x	m/x	m/x	m/x
$Al_2(SO_4)_3$...	8,192	16,384	65,536	131,072	1,048,576
$Al(NO_3)_3$...	1,024	16,384	65,536	131,072	1,048,576
$AlCl_3$...	2,048 ²	2,048 ²	65,536 ³	131,072 ³	131,072
$AlCl_3NaCl$...	16,384	32,768	65,536	131,072	131,072
$KAl(SO_4)_2$...	1,024	4,096	32,768	65,536	131,072
$NH_4Al(SO_4)_2$...	8,192	16,384	131,072	202,144	524,388

1. The concentration of aluminum in a $m/1,048,576$ $AlCl_3$ solution is 0.000,003 per cent.

2. The concentration of aluminum in a $m/2,048$ $AlCl_3$ solution is 0.001,3 per cent.

3. The concentration of aluminum in a $m/65,536$ $AlCl_3$ solution is 0.000,04 per cent.

4. About midway between $m/131,072$ and $m/65,536$. The concentration of aluminum in a $m/131,072$ $AlCl_3$ solution is 0.000,02 per cent.

These results showed clearly that compounds of aluminum, such as the chlorid, even when present in very minute proportions, are strong protoplasmic poisons and very toxic to growing plants.

III. MALLET'S EXPERIMENTS ON THE SOLUBILITY, IN GASTRIC CONTENTS, OF ALUMINUM COMPOUNDS CONTAINED IN BREAD MADE WITH ALUM BAKING-POWDER

Two years ago I was asked by Prof. J. W. Mallet to examine and discuss some results of Professor Mallet's investigation on the "solubility, in the stomach, of aluminum compounds contained in bread made with alum baking-powder." These results were summarized in the

2. House and Gies: *Am. Jour. Physiol.*, 1906, xv; *Proc. Am. Physiol. Soc.*, December, 1905, p. 19.

3. True and Gies: *Bulletin of the Torrey Botanical Club*, 1903, xxx, 390. Also Gies and Collaborators: *Biochemical Researches* 1903, i (reprint No. 37).