Clinical Studies of Renal Function by means of Phenolsulphonephthalein.

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The present paper was completed in August 1916.

Leaving London, where this work had been executed, I left the paper with Mr. Thomson Walker for publication. Lately he has written to me that he has not yet been able to get it published on account of the war influence and says:

"I have sent this article to the Quarterly Journal of Medicine again and asked them to reconsider this question of publishing it and have not heard from them yet.

I hope they have sufficient sense to publish it."

Under these circumstances I consider it suitable to publish it in this journal for the time being.

At this time I desire to express my great indebtedness to Mr. Thomson Walker for privileges and encouragement in connection with this work.

Introduction and General Considerations.

It has for a long time been recognised that in the investigation of renal disease, the ordinary routine examination of the urine does not afford a sufficiently accurate estimate of the pathological conditions present. A tumour of the kidney may, for instance, be present without any noticeable changes in the urine; pathological elements such as albumen, etc., may occur in the urine without necessarily indicating any serious renal disease.
Moreover if it is possible by such routine investigation of the urine to establish the presence and nature of a renal lesion, the extent of the damage inflicted on the functional activity of the organ remains still a matter o conjecture.

The estimation of renal function has in recent years been the subject of much research: many and various methods have been suggested dependent mainly on (i) the estimation in the urine of certain products of excretion and (ii) the estimation of similar substances retained in the blood.

The technique of many such methods is tedious and difficult; the idea method is one which affords the maximum amount of information with the minimum expenditure of time and energy.

One of the modern methods of renal functional diagnosis which claims to be more reliable than any of its predecessors, is the phenolsulphonephthalein test.

It has long been noticed that in cases of renal disease, the elimination of certain dyes introduced into the body is retarded and the amount excreted decreased. The methylene blue test as a means of estimating the permeability of the kidney was introduced in 1897 by Achard and Castaigne (2). The use of rosaniline as its substitute was proposed in 1898 by Lepine (23). Heidenhein's indigo-carmine was introduced into clinical medicine by Voelker and Joseph (40) in 1903 and this dye for a long time since has been very widely used.

Recently (1910) Rowntree and Geraphty (28) published from Young's clinic at Baltimore an investigation of the renal function by means of phenolsulphonephthalein. The work originated in the researches of Abel and Rowntree (1) upon the phthalein family.

Phenolsulphonephthalein is a bright red crystalline powder insoluble in ether, somewhat soluble in water, more so in alcohol, but readily soluble in solutions of sodium carbonate. Its dilute alkaline solution is of a purer red than that of phenolphthalein; while a more strongly alkaline solution is purple.
The presence of a sulfo group (SO₂) has increased according to Abel and Rowntree (1), the acidity and the power of salt formation of this phthalein and it is these properties which may render the drug excretable by the kidneys.

To obtain some general idea of the subject of this test, it may firstly be convenient to refer briefly to the technique and results of the test originally described by the authors (28).

**Technique.**

Twenty minutes to half-an-hour before commencing the test the patient is given 300 to 400 c.c. of water in order to ensure a free urinary secretion; a catheter is introduced into the bladder and the latter completely emptied; then, noting the time, one c.c. of the solution, containing 0.006 gm. of phenolsulphonephthalein is injected subcutaneously. Urine allowed to drain into a test tube containing a drop of strong sodium hydroxide solution and the time of appearance of the first faint pinkish tinge is noted. From this point the urine is collected over a period of two hours, the urine being collected at the end of the first hour and again at the end of the period. To each specimen sufficient NaOH is added to make the urine decidedly alkaline in order to elicit the maximum colour. The solution is now diluted up to a litre (or some proportionate amount as 500 c.c., 400 c.c., or 200 c.c., etc.) with distilled water and a small filtered portion is used to compare with the standard solution. This consists of 0.003 gm. of 'phthalein (or ½ c.c. of the solution used for injection) diluted up to one litre and made alkaline by the addition of one or two drops of strong NaOH solution.

The colorimetric readings are carried out by means of Dusbosq's colorimeter; with this instrument the authors could detect a difference of 0.04 mg. of 'phthalein.
The chief advantages of the test claimed by the authors are:
1. The complete elimination of the drug by the kidneys, its chemical nature being unchanged.
2. The early appearance of the drug in the urine following its administration.
3. The rapid excretion of the drug by the kidneys, necessitating observations over only a short time.
4. The brilliancy of colour, which is imparted to alkaline urine and which is not readily influenced by the colouring matter of the urine itself.
5. The facility with which this drug renders itself to colorimetric methods, making accurate quantitative estimation possible.
6. The simplicity of the technique for qualitative estimation.
7. The absolute non-toxicity and non-irritant nature of the drug locally.
8. The extreme smallness of the dose required and the assurance this gives of there being no extra strain placed upon the kidneys during the test.

They made numerous observations and arrived at the following conclusions:
1. In normal cases, the drug appears in the urine in from five to ten minutes, and forty to sixty per cent of the six milligram dose (the average being about fifty per cent) is recovered in the first hour and fifteen to twenty-five per cent in the second.
2. The permeability of the kidney for this drug is decreased in both chronic parenchymatous and interstitial nephritis, the decrease being most marked in the interstitial variety.
3. The test has proved to be of great practical value in revealing the true renal function in cases with prostatic obstruction. It is here of more value than the urinary output (total solids, urea, or total nitrogen) and enables the surgeon to select a time for operation when the kidneys are in good functional condition.
4. The improvement in cases of prostatic obstruction following the institution of preliminary treatment is strikingly demonstrated by the test and the time most suitable for operation is indicated.

5. In unilateral and bilateral kidney diseases the absolute amount of work done by each kidney as well as the relative proportion can be determined when the urines are obtained separately.

Since this new method was introduced a number of contributions upon this subject have been published by the American as well as Continental clinicians, while in English literature very few observations on these lines have been recorded up to the present time.

Mr. Thomson Walker noticed its clinical importance and suggested that I should undertake further work on the subject.

He very kindly placed at my disposal many interesting cases both at the Hampstead General Hospital and at St. Peter's Hospital, London.

Before recording my own observations, it seems fitting to refer to the literature devoted to this test.

A) 'Phthalein and experiment.——

Pharmacological studies of the drug were carried out by Abêl and Rowntree (1).

Eisenbury (13) studied its elimination in dogs, the subject of a variety of experimental renal lesions. He found that the 'phthalein test was one of the most satisfactory and at the same time most delicate methods of estimating the functional activity of the kidney. The elimination of the dye was decreased in so-called spontaneous nephritis and in experimental nephritis, etc., but it was increased in the presence of the renal lesion caused by nephrotoxic immune serum. For this discrepancy he could find no explanation.

Rowntree and Geraphty (28) noticed that the excretion of the drug does not run parallel to the excretion of urine and similarly, the output is not much influenced by the previous administration of different diuretics. These authors found experimentally in animals that those diuretics (caffeine,
urea, dextrose, phloridzin, calomel, etc.) which are thought to exert a stimulating influence on the cells of the renal tubules, slightly increase the 'phthalein output; whereas those diuretics like hypertonic sod. chloride, potassium nitrate and digitalis, which act entirely mechanically 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 noticed in man following the dosage usually administered for diuretic purposes, hourly estimation being made.

Behrenroth and Frank (6) confirmed the fact that diuretics do not affect the quantitative elimination of the dye, but they noticed its earlier appearance. Schwarz (33) records decreased elimination after intravenous injection of diluted hydrochlorie acid into rabbits.

Austin and Eisenbury (3) found that in dogs with experimental nephritis caused by uranium nitrate, potassium chromate or cantharidin, the decrease of the 'phthalein was in a general way, proportional to the dose of the poison, but bore no constant relation to the changes in the nitrogen or chloride elimination; a marked decrease occurred synchronously, as a rule, with the onset of the symptoms of intoxication (vomiting), and therefore they considered the 'phthalein test a better indicator of the renal ability to eliminate the toxic substance responsible for the symptoms of renal changes than the estimation of the total nitrogen or chloride excretion.

Rowntree and Geraphty (28), Schwarz (33) and Bachrach and Loewy (5) concluded from experimental evidence that the 'phthalein is excreted mostly by the tubules, but probably also to a slight extent by the glomeruli.

B) Modifications in the technique of the 'phthalein test.—

In their early work Rowntree and Geraphty administered the drug subcutaneously but later (29) they have employed the intramuscular and intravenous routes. The appearance of the dye following intramuscular injection is practically the same as after subcutaneous administration, but the output is found to be 5 to 10 per cent more for the first hour. Following intravenous injection, the drug normally appears in from 3 to 5 minutes,
and 35—45 per cent is eliminated during the first 15 minutes; 50—65 per cent in half-an-hour and 63—80 per cent during the first hour. For general use, however, the authors advocate injection into the lumbar muscles.

Eichmann (14) and Keyes and Stevens (22) recommend intravenous administration.

Geraphty (18) modified the technique of estimating total renal function as follows; after injection the patient is instructed to void urine at the end of one hour and 10 minutes and again at the end of two hours and ten minutes from the time of injection. In this method, no account is taken of the time of appearance of the dye, most importance being attached to the quantity excreted; the principle of this extremely simple method being based upon the fact that the drug should appear normally in about 10 minutes and this delay might be consequently allowed for. In cases with urinary obstruction a catheter must be employed.

Cabot and Young (10) and Dietsch (12) see no reason for giving water previous to the test, as the amount of water ingested bears no relation to the output of the drug.

To overcome the error in colorimetric estimation, due to the presence of urinary pigment or blood, Rowntree and Geraphty suggested to utilize the expedients:

1. The patient's own urine or any other specimen of the same colour in making up the standard solution.
2. Basic lead acetate to precipitate the normal colouring matter of the urine.

But Cabot and Young consider that the use of this salt reduces by 10—25 per cent the amount of the 'phthalein eliminated and therefore prefer the former method.

Whitney (42) proposed the interposition of a piece of fairly vivid yellow glass between the eye and the solutions to be compared.

In addition to Dubosq's colorimeter, Hellige's modified haemoglobinometer, Autenrith-Koenigsberger's colorimeter, or the simpler apparatus of
Cabot and Young (10), and Brotherhood (8) may be used for the colorimetric determination.

C) **The normal excretion of phthalein.**

In estimating renal function two separate problems have to be considered:

1. The estimation of the total function or the combined work done by the two kidneys.
2. The estimation of the separate function or the work done by each kidney.

The normal rate of excretion of the phthalein recorded by different authors varies slightly. This variation is dependent on several factors and the following Table summarizes the results obtained by different observers.

<table>
<thead>
<tr>
<th>Author</th>
<th>Colorimeter</th>
<th>Locality of injection</th>
<th>Appearance after injection</th>
<th>Per cent phthalein</th>
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<tr>
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<td>1 hr.</td>
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<tr>
<td>Rowntree &amp; Gersphyl (28)</td>
<td>Dubosq</td>
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<td>intravenous</td>
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<tr>
<td>Cabot &amp; Young (10)</td>
<td>Dubosq</td>
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<td>Hessel (21)</td>
<td>Authenrich, Koenigsberger</td>
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<td></td>
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<td>Urobel (39)</td>
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<td>Dietsch (12)</td>
<td>Authenrich, Koenigsberger</td>
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<td>Vogel (41)</td>
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<td>Rubner &amp; Fromme (32)</td>
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<td>Goodman &amp; Kristeller (19)</td>
<td>Dubosq</td>
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<td>Comrie (9)</td>
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<td>Mori (26)</td>
<td>Authenrich, Koenigsberger</td>
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<td>Sanford (36)</td>
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Deutsch (11) asserts that the renal function may be considered normal in cases where:

1. The amount of the drug excreted in the first half-an-hour is measurable.
2. The elimination reaches the maximum at the end of the first hour.
3. The elimination is complete (of course with measurable amount) within the first two hours (later being scarcely excreted but sometimes continuing for some hours).
4. The amount excreted in the first two hours is at least 50 per cent.

Behrenroth and Frank (6) considered as a criterion of normal function that the amount of the dye eliminated in the first hour should considerably exceed that eliminated in the second.

Comrie (9) formulated a rough general rule that in healthy cases the amount eliminated during the first hour should be at least equal to twice the amount excreted during the second and third hours.

**D) Abnormal excretion of phthalein.**—

In studying abnormal renal function, it seems convenient to classify the renal condition met with in the following three groups:

1. Medical cases—nephritis.
2. Non-medical bilateral cases, associated with obstruction in the urinary passages (e.g. prostatic cases).
3. Unilateral and bilateral surgical cases.

Heretofore, in medical cases, functional tests of the kidney have not been considered of any great value.

As has already been pointed out, Rowntree and Geraphty (28) applied the 'phthalein test in different kinds of nephritis, but did not find that increased permeability of the kidney to the drug which was shown by Bard to exist for methylene blue and by Dreyfus working with rosaniline. Consequently, the authors consider their method of great diagnostic and prognostic value in nephritis, inasmuch as it reveals the degree of functional
derangement, whether associated with the acute or chronic variety; and, moreover, the test is of value in cardio-renal cases in determining by what degree renal insufficiency is responsible for the clinical picture present. The test is not only valuable in differentiating uraemia from other similar conditions, but may also indicate that uraemia is impending when no clinical evidence of its existence is present.

Cabot and Young (10) found, in 26 cases of chronic nephritis that the average time of appearance of the 'phthalein was delayed as much as 25 minutes and the amount excreted in the first hour only reached 15.4 per cent and in the second 13.6 per cent in cardio-renal cases they confirmed the statement of previous authors, whilst in 8 cases of disease of the vascular system they found normal excretion.

Fischbein (16) recognised some general deficiency of renal function during the latter stages of scarlet fever. In cases of acute nephritis an increased output was observed in two, and a decreased output in one case. In several instances in which headache and nausea occurred (although no albumin was found in the urine) the test showed some decrease in the function of the kidney. Thus the author ascribed some practical value to the 'phthalein test in the treatment of scarlet fever, a disease so commonly complicated by nephritis.

Deutsch (11) concluded from observations of 36 different renal cases that the test was of great value in estimating the degree of the renal lesion; he considered that the drug was not excreted by the tubules exclusively as he found no difference in elimination between parenchymatous and interstitial nephritis.

Geraphty (18) records a striking case in which the 'phthalein excretion was 7 per cent for two hours, although no suspicion of any renal disease was entertained. A few months later the patient suddenly developed uraemia which ended in death; autopsy revealed an extreme degree of chronic interstitial nephritis.

In 35 autopsies the same author verified the accuracy of the test (in
one case only of bilateral polycystic disease had the test been normal). He found also that in the milder forms of so-called glomerular nephritis and in mild parenchymatous nephritis the definite clinical evidence of renal disease seemed at first rather irreconcilable with the relatively high 'phthalaein output. This he explains on the grounds that the drug is eliminated chiefly, if not entirely, by the tubules, so that the presence of glomerular disease would not necessarily cause decreased 'phthalaein output.

Dietsch (12) confirmed the differential diagnostic value of the test, especially in cardio-renal cases, and pointed out the ease with which the test could be performed in a minimum amount of time both before and after the administration of cardiac stimulant.

According to Rowntree and Fritz (30) it is possible in cases of cardio-renal diseases associated with varying degrees of chronic passive congestion and nephritis to determine which factor is of greater importance in the causation of the clinical picture encountered. The test, moreover, must readily be repeated.

Goodmann (20), in summarizing the information gained in his observations on miscellaneous cases such as lobar pneumonia, influenza, typhus, diabetes, gastric carcinoma, besides nephritis and surgical urinary cases, called attention to the following points:

1. In clinical influenza the small output of 'phthalaein is not in keeping with the findings in other general diseases.
2. The general series of diseases show a good output of 'phthalaein as a rule when there is clinically no evidence of renal involvement.
3. The findings in regard to the value of the test in nephritis both from a diagnostic and prognostic standpoint confirm former conclusions in this respect, and also the statement of Rowntree and Geraphy, that the test reveals the degree of functional derangement, whether the nephritis be acute or chronic.
4. In several cases this test has revealed a degree of renal insuffi-
ciency, of which the clinical condition of the patient gave no
evidence, but the existence of which was confirmed by the fatal
issue of the cases.

Baetjer (4), however, disapproved of the test on the ground that in
three out of his four cases of chronic nephritis, the phthalein output was
well above normal. Consequently, he concluded:

1. That there exist cases of well-marked nephritis with evidence of
   impairment of renal function, in which certain tests reveal an
   eliminative power normal or even above normal.
2. These cases may be more common than has been supposed.
3. There may exist in some types of nephritis a stage in which the
   kidney is hyperpermeable at least to some substances used for
   functional tests.
4. Therefore the renal function should be determined by different
   methods.

Behrenroth and Frank (6) working with chronic interstitial nephritis,
experienced a marked delay of the first appearance of the phthalein,
averging 22 minutes and a considerable decrease of the amount excreted in
two hours about 5 per cent. But special value of the test was found in
the diagnosis of cardio-renal cases. The authors suggested that a con-
siderable decrease in chronic nephritis might be due to co-existent derange-
ment of other organs, probably of the liver.

The results of the test in cases of acute parenchymatous nephritis were
similar.

Widal, Weill and Vallery-Radot (44) report a comparative study of
the results of the phthalein test and of urea excretion in nephritis and con-
clude that the test and Ambard’s ureo-secretory coefficient yield similar
clinical information.

Frothingham and Smillie (17) confirmed the statements of previous
authors, but considered the estimation of non-protein nitrogen in the blood
of more prognostic value, as the latter is not influenced by cardiac failure
and other unknown factors as is the case with the 'phthalein test.

Thayer and Snowden (37) published a series of the fatal cases occurring in the medical wards of the John Hopkins' Hospital, in which after the 'phthalein test had been made during life, a necropsy with careful microscopical study of the kidney had followed. Their investigations shew that:

1. In severe chronic nephritis the 'phthalein test indicated a uniformly low output, which, as a rule, in those instances not interrupted by an acute terminal process, decreased steadily up to the onset of uraemia, and was nearly or wholly suppressed from a day or two to a month before death.

Acute terminal processes which may be unexpected clinically, are common and in such cases a sudden elimination in the excretion of the 'phthalein may come on in cases where the percentage previously excreted is not so low as to appear menacing.

2. In not a single instance, and indeed not once in all investigations made during the last 5 years, have they met with a case of severe chronic nephritis with a good 'phthalein elimination.

3. In chronic passive congestion (cardiac disease) the result of the test often showed a considerable reduction in the two hours' elimination of the 'phthalein. In marked cardiac failure the 'phthalein output may be reduced to but a trace in two hours; but the excretion is, as a rule, rapidly restored with the re-establishment of circulatory compensation.

4. These observations tend to support their previous impress, in that the 'phthalein test was a procedure of considerable diagnostic and prognostic value, especially in the study of chronic nephritis.

Comrie (9) reports a series of investigations in this respect which may be summarised as follows:
In diabetes mellitus, the author constantly found that the amount excreted in three hours was reduced to 30 or 40 per cent. This phenomenon is, as he describes it, apparently due to a vital defect of the kidney function as the 'phthalein when left in solution in diabetic urine for several days undergoes no diminution. In addition, he calls attention to two striking cases of advanced parenchymatous disease, in which a very bad prognosis could be given from the fact that the three hours' secretion was 3 per cent in the one case and 1 per cent in the other. In the former case the patient died in about 2 weeks; the other within 48 hours.

Consequently the author formulated a rough general rule, as has already been suggested, that in healthy cases the amount excreted during the first hour should be at least equal to twice the sum of the amounts excreted during the second and third hours (total 75 per cent or over); in cardiac cases with poor blood pressure, the first hour's quantity equalled the sum of that in the second and that in third hour (though the total might be reduced to half the normal); in interstitial nephritis the first hour's quantity was about equal to that of the second, but less than that in the second and third together (total quantity high). In advanced parenchyma-
tous degeneration, the amount excreted in the first hour was less than in the second (and the total was very low—30 per cent).

Elliot (15) substantiated the importance of the test in medical cases generally, but doubted whether the test can be employed to any important extent in the diagnosis of nephritis. He drew attention to a point of possible importance in the interpretation of defective function response to chronic nephritis with the occasional existence of sub-acute exacerbations where the 'phthalein may be reduced, and the fact that excretory response of the kidney to the test is on the average higher in ambulantory cases tested in office practice, than in hospital. He agrees with the statement of Miller and Cabot (27) that the excretory function is inclined to diminish with the age.

2. Non-medical bilateral cases, associated with obstruction in the lower urinary tract (e.g. prostatic cases).

The renal condition in cases of obstruction in the lower urinary tract, especially in cases of prostatic hypertrophy, has received little attention in the past, although the development of uraemia following surgical intervention in this type of case, with frequently fatal consequences, has long been recognised.

As a result of obstruction in the lower urinary tract, pathological changes of destructive or temporary nature and dependent on mechanical or toxic conditions, occur in the kidney.

Functional tests of the kidney in this type of case are so important that to omit them is to court disaster when adopting surgical measures.

It is scarcely possible by the ordinary routine methods of examination, however, to obtain an accurate picture of the renal condition of these patients. For this purpose cryoscopy of blood, the indigo-carmine test and the determination of urea retention in the blood, have been chiefly utilised.

Mr. Thomson Walker (38) found that in these cases, the excretion of methylene blue is retarded, the dye frequently does not appear for three, or three and a half hours and is often excreted for a period of eight to
ten days following an injection, while in several instances it does not appear at all.

Now, concerning the phthalein test in these cases, Rowntree and Geraphty (28) in their study of 53 cases of enlarged prostate, representing all stages of the disease, found the test of much value and came to the following conclusions:

1. In general, it has been found that cases in which the obstruction was of short duration and in which the residual urine was small, and also in cases leading a regular catheter life, a practically normal and only slightly delayed time of appearance was obtained, while the quantity of drug excreted was only slightly diminished.

But the cases of long standing, associated with a large amount of residual urine and not leading a regular catheter life, showed a marked retardation in the time of appearance of the drug and a decided decrease in the amount eliminated.

In short, in the majority of the cases, the test indicates a more or less degree of renal impairment.

2. 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.

3. When there is a free urinary excretion, a delay beyond twenty to thirty minutes in the time of appearance of the dye is suggestive of marked decreased permeability of the kidney.

A marked decrease in the amount excreted almost 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 pyelo-nephritis, improvement will usually follow as a result of the treatment and will be indicated by a decrease in the time of the appearance of the dye and simultaneously an increase in the amount eliminated.

The above statement of Rowntree and Geraphty was substantiated by Cabot and Young (10) who (in 25 cases of obstruction due to prostatic hypertrophy) noticed usually a delayed time of appearance, averaging about 22 minutes and a low output of 26 per cent in two hours; while in cases of urethral stricture (8 cases) a better renal condition was detected, though many of the cases were past middle life.

The findings of Vogel (41), Goodman (20), Sanford (36), Blum (7) were again in line with those of the previous authors.

Bachrach and Loewy (5) noted a parallelism between the elimination of indigo-carmine and phthalein in 15 cases of urinary obstruction.

Rowntree, Geraphty and Marshall (31) carried out an investigation of renal function in 43 cases of urinary obstruction (mostly prostatic) by means of the lactose, diastase, blood urea and cryoscopy tests in association with the phthalein test. They concluded that the phthalein affords an indispensable index to the true renal condition in detecting the functional impairment in this type of urinary diseases and that nothing beyond corroborative evidence is to be obtained from the employment of other functional tests.

3. Surgical renal cases.

"When one kidney is diseased, and it is accepted that its function is seriously impaired or totally destroyed, the question of prognosis, and the decision in regard to surgical interference and its extent, will in a considerable majority of cases depend upon the view which is taken in regard to the functional activity of the second kidney" (Thomson Walker). Thus, before one kidney can be removed, the ability of the sister organ to take up all its functions must be assured and before conservative operation as
nephrectomy or pyelotomy are undertaken, consideration must be given to the role of the diseased kidney in the maintenance of renal function. This may be of such little significance as to render the removal of the whole organ justifiable: on the other hand, it may be playing such an important part in the maintenance of renal function as to make its preservation imperative. Decision in such cases can only be arrived at by utilising methods which will demonstrate (i) the maximum functional capacity of the sound kidney to compensate the loss of function caused by the removal of its fellow, and (ii) the extent of the functional impairment of the diseased organ.

Such knowledge, however, with our present methods of examination is not obtainable and we must be content with determining:

i. Whether a kidney is functioning normally at the time of examination, and

ii. Whether it is possible for a kidney to increase its excretory function.

Information on the first point is chiefly afforded by the routine method of analysis of a specimen obtained by ureteric catheterisation—functional tests furnishing information on the second point.

The diagnosis on purely clinical grounds for surgical affection of the kidney may be a matter of great difficulty; and the solution of the problem may be found in the results of a functional test.

Thomson Walker (38) has pointed out that along with disease of one kidney, there may be in progress a compensatory hypertrophy of the sound kidney sometimes associated with pain, tenderness and palpable enlargement. Such kidneys have on occasions been the object of exploration and even of nephrectomy.

In unilateral tuberculosis also ureteric catheterisation may show that the urine from the supposed sound kidney contains albumen and casts. The pathological condition in such a case may be of a temporary nature only—some toxic degenerative affection of the tubular epithelium caused by the circulation of the toxins of the tubercle bacilli. On the other hand it may
be of long standing and permanent, as when unilateral tuberculosis develops in chronic Bright's disease (Blum).

Finally, it may be pointed out that the absence of local signs of disease of the second kidney is no proof that it is healthy or even existent.

In 93 cases collected from the literature by Thomson Walker in which death, due to uraemia or anuria closely followed an operation upon a kidney, the second kidney was found absent in 10 and completely atrophied in 8 cases.

In such cases as have been mentioned above, a properly performed functional test would greatly assist the surgeon in diagnosing the condition present and prevent unfortunate errors in treatment.

Where ureteric catheterisation is possible, the solution of many surgical problems may be found in the phthalein test. Occasionally, and especially in tuberculosis, it is found impossible to pass a ureteric catheter.

Legueu (24) met with this difficulty in 22 of 70 cases of renal tubercle. In such cases when it is clinically obvious that the disease is unilateral and when at the same time the total function as revealed by the phthalein test is found normal, compensatory hypertrophy, i.e., functional soundness of the second kidney, may be assumed especially in cases in which the functional capacity of the diseased organ is wholly destroyed. A subnormal total function would, on the other hand, indicate the inefficiency of the second kidney.

Rowntree and Geraphty (28) applied the phthalein test to surgical disease of the kidney in association with ureteral catheterisation: Twenty minutes previous to the test 600 to 800 c.c. of water is given to patient; the ureters are catheterised and the drug injected; the collection of urine is then continued for an hour, starting from the time when the drug first appears in the urine.

Their data obtained with the test are as follows: In normal cases the time of appearance of the drug from the two sides has been almost always the same (in the majority of cases it appears in 5—10 minutes). Occasion-
ally a slight difference in elimination time of 2-3 minutes has been noted.

In over 40 cases of unilateral or bilateral renal infection, they obtained valuable information as to the absolute and relative amount of work done by each kidney. But they concluded that the amount of delay in the time of appearance was comparatively of little value; reliance being chiefly placed upon the quantity excreted during a period of at least one hour.

In a later publication, (29) the same authors admit that the test is not always mathematically accurate, but still contend that the test indicates better than any other the degree of functional renal capacity.

In the majority of cases examined by Keys and Stevens (22) the urea estimation and the phthalein test gave much the same results and indicated the same ratio of functional ability for the two kidneys.

In a later paper they published observations on 26 cases in which intravenous injection of the phthalein was employed. They may be summarised as follows:

1. Phthalein output seems to be little, if at all influenced by oliguria or polyuria.

2. Phthalein percentage agrees very closely with the urea elimination in centigrammes (Urea percentage multiplied by c.c. of urine).

3. The delay in the appearance of the drug varies widely.

The most striking feature of the delay is that it may be approximately equal for 2 kidneys, whose function differs widely. Hence the delay, whether absolute or relative is peculiarly misleading and should be taken into consideration for the purpose of estimating the time at which to begin collecting urine.

4. Inhibited elimination of the drug which has often been noticed after intramuscular injection, has seldom occurred after intravenous administration. Indeed, so rapid is the output of phthalein following intravenous injection that accurate readings can almost invariably be obtained in 10 to 15 minutes after the appearance of the drug.
5. Roughly speaking, an excretion of 1 per cent in one minute for the first 10 or 15 minutes is normal.

Smith (34) summarizes his work in connection with the 'phthalein test in surgical disease as follows:

After the intravenous injection of 0.006 mg. 'phthalein each kidney of a normal pair begins to excrete the dye in about three minutes and in the next 15 minutes puts out about 15 per cent. If a sound kidney which has a diseased fellow, excretes 15 per cent in the same period, it is at least equal to one normal kidney; if more than that, it is already taking up the work of both. Neither the time of the appearance of the dye, nor the amount excreted is materially influenced by the passage of ureter catheter, and the results of the test agree with great constancy with actual pathological conditions in the kidney.

Sanford (36), Behrenroth and Frank (6) recognised the value of the test in surgical renal cases.

Geraphty and Rowntree (29), and Geraphty, Rowntree and Cary (30) record a series in which the diastase test and urea estimations were combined with the 'phthalein test and conclude that:

1. The diastase test is of value in the majority of cases in indicating which is the diseased or more diseased kidney.
2. In the majority of instances it is not necessary and adds nothing to the information obtainable from the 'phthalein or urea determination—both of which are more easily accomplished.
3. In cases with leakage or serious catheter inhibition, but where sufficient urine to allow a diastase determination has been obtained.
4. Dilution affects the urinary diastase content to a less extent than it does urea per cent.

Blum (7) objects to the test for the reason that the accuracy of the quantitative estimation of the drug suffers from the impossibility of securing absolutely close contact of the ureter against the catheter. Moreover, it is almost impossible in practice to leave the catheter in position for two hours.
in more than one in a hundred cases. He is of the opinion that the value of the test lies not so much in estimating the renal function for the purpose of surgical indications in unilateral renal complaints, as in determining the conditions of salt excretion in non-surgical renal diseases.

Urobel (39) Sugimura (35) agree with this view. The latter claims that the colorimetric reading is frequently inaccurate in cases where there is haematuria—a frequent occurrence in association with ureteric catheterisation.

My own Observations.

On more than fifty different subjects investigations have been carried out.

The methods employed in the present work are those originally described by Rowntree and Geraphty with a few modifications.

Total Function—technique adopted.

1. Patients void urine immediately before the test.
2. One c. c. (17 minims) of the phthalein solution, containing 0.006 gram of the drug (prepared by Allen & Hanbury) is injected deeply into the muscles (generally lumbar muscles) with an ordinary hypodermic syringe.
3. Patients are instructed to void urine at the end of one hour and ten minutes, and again at the end of the two hours and ten minutes from the time of injection and so on for four hours.
4. Each specimen is kept separately, and is examined as soon as possible to prevent any loss in the amount of the drug present (especially when the urine is alkaline).
5. To each measured specimen sufficient NaOH solution is added to elicit the maximum colour. The urine is diluted with distilled water up to 1000, 500 or 250 c. c. etc., and a small portion is filtered.
6. Colorimetric determination is carefully made with Dubosq's or Laurant's
colorimeter, using diffused daylight (in my early work Autenrith-Koenigsberger's colorimeter was utilised).

7. Standard solution was prepared as follows:
   One c. c. of the phthalein solution of the same sample as is used for the experiments is introduced into a 1000 c. c. measuring flask and the flask filled up to the neck with distilled water, a few drops of strong NaOH solution being added. This solution can be kept for a long time.
   This solution is frequently too strong for the purpose of comparison and is, therefore, diluted with an equal quantity of distilled water when used.

8. To overcome the fallacy in colorimetric readings due to the presence of urinary pigment, patients' own or others' urine has been found most satisfactory in diluting the standard solution.
   If there is haematuria, the specimen is carefully heated to coagulate the albumin; made up to the original quantity and filtered.

9. The precaution of administering water before the examination has not been particularly taken into consideration, except in cases of manifest oliguria.

10. In case of urinary obstruction, as well as in female patients, the catheter has been employed.

11. The urea content of the urine was determined by both Gerrard's apparatus and by Marchall's (25) original methods. The principle of Marchall's method consists in the conversion of the urea into ammonium carbonate by means of the soy bean enzyme and the titration with standard hydrochloric acid in the presence of methyl orange.

12. Creatinine was determined by Folin's method: Urine is treated with picric acid and caustic soda. The intensity of the colour thus produced is compared with that of a standard solution of potassium dichromate by means of Dubosq's colorimeter.

13. The diastatic power of the urine was estimated by Wohlgemuth's (43)
method, varying amounts of urine being treated with a given amount of soluble starch for 30 minutes at 38°C.

A. Non-renal cases—Table I.

In 9 different patients suffering from conditions not involving the kidneys, 'phthalein tests have been made.

From 45 to 66 per cent of the 6 milligram dose, the average being 56 per cent, was recovered in the first hour; from 16 to 27 per cent, the average being 22 per cent, in the second hour. The total amount excreted in the two hours was 71 to 88 per cent, the average being 78 per cent. In the third hour 8 per cent was eliminated, while in the fourth a 4 per cent average was recovered.

From this result we may propose a rough general rule that in normal renal cases the amount for the first hour should be at least equal to twice the sum of that for the second, the total for the two hours being about 78 per cent, whilst in the majority of instances excretion is practically complete at the end of four hours.

The procedure of excretion in normal cases may be shown by the appended diagram (Fig. 1).

FIGURE 1.

'Phthalein output' in normal kidneys.
### Table I.
#### Non-Renal Cases.

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Urine (24 hours specimen)</th>
<th>Phenolsulphonephthalein test (per cent)</th>
<th>Phthalein Index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Amt. c.c.</td>
<td>Reaction</td>
<td>Sp. Gr</td>
</tr>
<tr>
<td>1.</td>
<td>F. S. M.</td>
<td>M</td>
<td>51</td>
<td>Carbuncle of Neck</td>
<td>2000</td>
<td>Acid</td>
<td>1010</td>
</tr>
<tr>
<td>2.</td>
<td>B. A. M.</td>
<td>M</td>
<td>45</td>
<td>Fracture of Tibia</td>
<td>1250</td>
<td>Acid</td>
<td>1015</td>
</tr>
<tr>
<td>3.</td>
<td>F. F. M.</td>
<td>M</td>
<td>38</td>
<td>Inguinal hernia</td>
<td>1800</td>
<td>Acid</td>
<td>1018</td>
</tr>
<tr>
<td>4.</td>
<td>M. S. M.</td>
<td>M</td>
<td>42</td>
<td>Varicose Veins</td>
<td>2200</td>
<td>Acid</td>
<td>1015</td>
</tr>
<tr>
<td>5.</td>
<td>G. O. M.</td>
<td>M</td>
<td>69</td>
<td>Bronchitis</td>
<td>860</td>
<td>Acid</td>
<td>1023</td>
</tr>
<tr>
<td>6.</td>
<td>S. P. M.</td>
<td>M</td>
<td>50</td>
<td>Fracture of femur</td>
<td>1560</td>
<td>Acid</td>
<td>1012</td>
</tr>
<tr>
<td>7.</td>
<td>E. L. F.</td>
<td>M</td>
<td>38</td>
<td>Chronic Appendicitis</td>
<td>1240</td>
<td>Acid</td>
<td>1018</td>
</tr>
<tr>
<td>8.</td>
<td>W. E. M.</td>
<td>M</td>
<td>49</td>
<td>Gall Stones</td>
<td>1500</td>
<td>Acid</td>
<td>1020</td>
</tr>
<tr>
<td>9.</td>
<td>H. H. M.</td>
<td>M</td>
<td>43</td>
<td>Hydrocele</td>
<td>2240</td>
<td>Acid</td>
<td>1010</td>
</tr>
</tbody>
</table>
A glance at Table I will be sufficient to substantiate the statement of other authors that the excretion of the drug does not run parallel with the amount of urine excreted.

B. **Medical renal cases**—Table II.

In this series a few cases of nephritis and cardiac failure have been observed. It would be presumption to conclude much from this small number of observation, but it seems justifiable to say that in nephritis as well as in certain instances of circulatory disturbances the elimination of the drug is definitely diminished, not only in absolute amount, but in the rapidity with which it is excreted. The chief point seems to be that in this group the amount eliminated during the first hour approaches the amount eliminated during the second, and in the majority of cases the greater amount is eliminated during the second hour. The mode of elimination in this type of case may be seen in the following curves (Fig. 2).

![Figure 2](image-url)
TABLE II.

MEDICAL RENAL CASES.

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Sex</th>
<th>Age</th>
<th>Clinical Diagnosis</th>
<th>Urine (24 hours specimen):</th>
<th>Daily output gms.</th>
<th>Phthalaein test (per cent)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Amt. c.c.</td>
<td>Reaction</td>
<td>Sp. Gr.</td>
<td>Albu- min</td>
</tr>
<tr>
<td>10.</td>
<td>J. A. F.</td>
<td>M.</td>
<td>32</td>
<td>Chronic parenchymatous Nephritis.</td>
<td>1700</td>
<td>Acid</td>
<td>1010</td>
<td>0.5</td>
</tr>
<tr>
<td>11.</td>
<td>R. E. M.</td>
<td>M.</td>
<td>20</td>
<td>Acute parenchymatous Nephritis.</td>
<td>1070</td>
<td>Acid</td>
<td>1018</td>
<td>0.7</td>
</tr>
<tr>
<td>12.</td>
<td>K. K. M.</td>
<td>M.</td>
<td>42</td>
<td>Acute parenchymatous Nephritis.</td>
<td>1250</td>
<td>Acid</td>
<td>1020</td>
<td>5.0</td>
</tr>
<tr>
<td>13.</td>
<td>J. S. M.</td>
<td>M.</td>
<td>48</td>
<td>Hepatic cirrhosis</td>
<td>1200</td>
<td>Acid</td>
<td>1020</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Renal cirrhosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiac Sclerosis.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.</td>
<td>F. T. M.</td>
<td>M.</td>
<td>53</td>
<td>Cardiac Dilatation.</td>
<td>1150</td>
<td>Acid</td>
<td>1025</td>
<td>+</td>
</tr>
<tr>
<td>15.</td>
<td>M. M. O.</td>
<td>M.</td>
<td>35</td>
<td>Mitral Stenosis.</td>
<td>1250</td>
<td>Acid</td>
<td>1010</td>
<td>+</td>
</tr>
<tr>
<td>16.</td>
<td>P. W. M.</td>
<td>M.</td>
<td>45</td>
<td>Oedema of legs following pneumonia.</td>
<td>2716</td>
<td>Neutral</td>
<td>1008</td>
<td>—</td>
</tr>
<tr>
<td>17.</td>
<td>G. H. F.</td>
<td>M.</td>
<td>37</td>
<td>Chronic bronchitis. Hepatic cirrhosis.</td>
<td>1520</td>
<td>Acid</td>
<td>1015</td>
<td>+</td>
</tr>
<tr>
<td>18.</td>
<td>N. J. M.</td>
<td>M.</td>
<td>59</td>
<td>Pyuria Cystitis.</td>
<td>2200</td>
<td>Acid</td>
<td>1010</td>
<td>+</td>
</tr>
</tbody>
</table>

Remarks:
- Hyaline granular casts Pus cells, Red Blood Corpuscles.
- Many red blood corpuscles Hyaline and granular casts Relieved.
- Granular and Hyaline, casts phthisis in cipiens. Died.
- Ascites Granular and Hyaline casts.
- No casts. Died Autopsy.
- Dropsy of the lower limbs Relieved.
- Ascites, Cyanose, Pus cells red blood corpuscles, no casts.
- Pus cells, coliform Bacilli No Casts.
N. B. In case 12 the elimination is practically nil and the patient died of uraemia about 2 months after the examination.

Case 14. A patient with cardiac dilatation who died suddenly. The excretory power on the day preceding death was greatly diminished (vide Table II).

From these observations it may be presumed that an extremely diminished elimination in nephritis or in cardiac failure is of grave prognostic significance and suggests impending death.*

**TABLE III.**

<table>
<thead>
<tr>
<th>Date</th>
<th>Clinical condition</th>
<th>Phthalein test (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>I. hr.</td>
</tr>
<tr>
<td>Case 15</td>
<td>Mitral stenosis Oedema of lower limbs</td>
<td>21</td>
</tr>
<tr>
<td>24. 3. 16</td>
<td>Dyspnoe.</td>
<td></td>
</tr>
<tr>
<td>10. 5. 16</td>
<td>Improved general condition.</td>
<td>45</td>
</tr>
<tr>
<td>Case 16</td>
<td>Oedema of lower extremities post</td>
<td>11</td>
</tr>
<tr>
<td>14. 2. 16</td>
<td>pneumonia.</td>
<td></td>
</tr>
<tr>
<td>9. 3. 16</td>
<td>General improvement.</td>
<td>50</td>
</tr>
</tbody>
</table>

The above Table (III) shows that in certain instances of circulatory disturbance, the clinical improvement is associated with an improvement in renal function as revealed by the 'phthalein tests.

A discrepancy will be found in Case 18, in which, although no other clinical symptoms were detected than those of a cystitis, nevertheless there was a definite diminution in excretory power. In this case two possibilities can be considered:

1. The presence of a latent pathological condition in the kidney (e.g., chronic nephritis).
2. The fact that the patient had been taking acid phosphate of soda with Hexamine (a factor which may hinder elimination).

It will be remembered that a decreased elimination of the 'phthalein was recognised by Schwarz (33) working with rabbits to which dilute hydrochloric acid had been given, but further investigations are required to
ascertain whether sod. acid phosphate decreases the elimination of the dye in the same manner as injection of hydrochloric acid does.

Before leaving the study of this type of case, it may be emphasised that a decrease of the excretion of the 'phthalein occurs, not only in renal impairment, but in extrarenal cases, especially in cardiac and hepatic diseases.

C. Non-medical renal cases associated with urinary obstruction
(prostatic hypertrophy)—Table IV.

This group includes seven cases of prostatic hypertrophy, one case of uraemia following prostatectomy and a case of urethral stricture. The functional tests were done in each case before surgical intervention, except in Case 22.

In general, the total renal function was decreased from 10 to 67 per cent for the two hours, averaging 44 per cent.

From Table IV the appended diagraphic chart was obtained, which gives a general idea of the excretory function of the kidney in urinary obstruction (Fig. 3).

FIGURE 3.

In the majority of instances, the test has revealed an impairment of function proportional to the duration of the disease, to the quantity of the residual urine, and to a neglected catheter life.
<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Urine (24 hours specimen): Daily output grammes</th>
<th>Phthalein test (per cent)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Amt. c. e.</td>
<td>Reaction</td>
<td>Sp. Gr</td>
</tr>
<tr>
<td>19.</td>
<td>C. H.</td>
<td>M.</td>
<td>77</td>
<td>Prostate Hypertrophy</td>
<td>1370</td>
<td>Alkaline</td>
<td>1015</td>
</tr>
<tr>
<td>20.</td>
<td>S. S.</td>
<td>M.</td>
<td>75</td>
<td>Prostate Hypertrophy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21.</td>
<td>G. P.</td>
<td>M.</td>
<td>53</td>
<td>Prostate Hypertrophy</td>
<td>1850</td>
<td>Acid</td>
<td>1010</td>
</tr>
<tr>
<td>22.</td>
<td>A. B.</td>
<td>M.</td>
<td>64</td>
<td>Uremic Condition after</td>
<td>900</td>
<td>Acid</td>
<td>1020</td>
</tr>
<tr>
<td>23.</td>
<td>R. B.</td>
<td>M.</td>
<td>45</td>
<td>Prostate Hypertrophy</td>
<td>1150</td>
<td>Acid</td>
<td>1018</td>
</tr>
<tr>
<td>25.</td>
<td>T. N.</td>
<td>M.</td>
<td>58</td>
<td>Prostate Hypertrophy</td>
<td>1800</td>
<td>Alkaline</td>
<td>1015</td>
</tr>
<tr>
<td>27.</td>
<td>H. H.</td>
<td>M.</td>
<td>64</td>
<td>Urethral Stricture Vesical Calculus</td>
<td>1100</td>
<td>Acid</td>
<td>1018</td>
</tr>
</tbody>
</table>
The functional improvement after a radical operation (prostatectomy) is easily revealed by the test, enabling us at the same time, to differentiate cases with destructive renal impairment from those with temporary functional disturbance (Table V).

**TABLE V.**

<table>
<thead>
<tr>
<th>Condition at the time of examination</th>
<th>Phthalein test (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I. hr.</td>
</tr>
<tr>
<td>Case 21 Before operation</td>
<td>42</td>
</tr>
<tr>
<td>5 weeks after operation</td>
<td>65</td>
</tr>
<tr>
<td>Case 25 Before operation</td>
<td>25</td>
</tr>
<tr>
<td>4 weeks after operation</td>
<td>58</td>
</tr>
<tr>
<td>Case 27 Before operation</td>
<td>11</td>
</tr>
<tr>
<td>4 weeks after operation</td>
<td>52</td>
</tr>
</tbody>
</table>

It is very difficult to indicate the possible minimal functional activity which would assure safety in surgical procedure.

In the majority of my series the radical operation (prostatectomy) has been followed by a favourable result, even in cases with extremely diminished renal function, as is shewn in Table IV. Nevertheless, it seems advisable to take precautionary measures in cases of urinary obstruction, i.e., in prostatic hypertrophy, with an extremely decreased function of the kidney, as in Case 19. These may take the form of regular catheterization or a preliminary cystotomy with drainage. In this respect, the test affords most valuable assistance in indicating the propitious time for surgical intervention.

**D. Surgical renal cases** (Estimation of the total function)—Table VI.

In 16 different unilateral and bilateral renal diseases the phthalein test has been applied. In the majority of cases of unilateral renal calculus and of tuberculosis (Cases 28, 29, 31, 37, 38) the total renal function has been found normal, showing satisfactory compensation for the damage to the renal parenchyma. In other cases of unilateral disease (Cases 30, 33, 34, 36) an
<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Urine (24 hours specimen): Daily output grammes.</th>
<th>Ammt. c. c.</th>
<th>Reaction</th>
<th>Sp. Gr.</th>
<th>Albumen</th>
<th>Urea</th>
<th>Creatinin</th>
<th>Diasonate 38°50'</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>F. A.</td>
<td>M</td>
<td>37</td>
<td>Renal Calculi (unilateral)</td>
<td></td>
<td>1580</td>
<td>Alkaline</td>
<td>1018</td>
<td>-</td>
<td>24.0</td>
<td>1.00</td>
<td>10.0</td>
</tr>
<tr>
<td>29</td>
<td>B. H.</td>
<td>F</td>
<td>22</td>
<td>Renal Calculi (unilateral)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>M. F.</td>
<td>M</td>
<td>40</td>
<td>Renal Calculi (unilateral)</td>
<td></td>
<td>1200</td>
<td>Alkaline</td>
<td>1020</td>
<td>+</td>
<td>22.5</td>
<td>0.95</td>
<td>6.6</td>
</tr>
<tr>
<td>31</td>
<td>M. F.</td>
<td>M</td>
<td>42</td>
<td>Renal Calculi (unilateral)</td>
<td></td>
<td>1540</td>
<td>Acid</td>
<td>1018</td>
<td>-</td>
<td>30.2</td>
<td>1.15</td>
<td>10.0</td>
</tr>
<tr>
<td>32</td>
<td>W. S.</td>
<td>M</td>
<td>50</td>
<td>Renal Calculi (bilateral)</td>
<td></td>
<td>1600</td>
<td>Alkaline</td>
<td>1010</td>
<td>+</td>
<td></td>
<td></td>
<td>5.0</td>
</tr>
<tr>
<td>33</td>
<td>C. O.</td>
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<td>Renal Tumour (unilateral)</td>
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<td>M</td>
<td>32</td>
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## VI. RENAL CASES

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<th>Remarks</th>
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<td>58</td>
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<td>15</td>
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</table>
Impairment of renal function has been demonstrated.

From the study of this series, the following data may be extracted:

Case 32.—Bilateral calculi. Prostatic hypertrophy. Residual urine 400 c.c. Radiography shows numerous calculi in the left kidney and a gigantic stone in the right. The total function of the kidney practically nil, as indicated by the ’phthalein test. Patient developed a uraemic condition.

Case 33.—Patient was treated for more than 2 months, the case being wrongly diagnosed as one of pyelitis. An occasional test revealed impairment of renal function, resulting in further investigation, when an advanced pyo-nephrosis was found. Nephrectomy. Recovery.

Case 34.—Clinically a case of a unilateral renal tumour, in which a marked diminution of the total function is obvious. In this case it may be surmised that the destructive process in the diseased kidney is too rapid to allow the opposite kidney to compensate the loss of renal tissue.

Case 36.—Clinically unilateral renal tuberculosis with a moderately delayed elimination of the ’phthalein. Unilateral nephrectomy showed an advanced stage of disease. In such a case it seems justifiable to consider the problem of defective elimination from three different standpoints. There may be (1) an unsatisfactory compensatory hypertrophy of the sound kidney, owing to the rapidity of the destructive process in the sister organ, (2) a nephritis of the second kidney resulting from the toxins of the tubercle bacillus produced by the first organ, or (3) bilateral tuberculosis.

Case 40 shows sufficient compensation with a solitary kidney after unilateral nephrectomy, whilst Case 41 points to insufficient compensatory function even 6 months after a nephrectomy for a tuberculous kidney.

In the latter case, an existence of tuberculosis in the remaining kidney is suspected.

Table VII demonstrates a gradual recovery of renal function after unilateral nephrectomy.
TABLE VII.

<table>
<thead>
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<th>Case 42</th>
<th>Condition at the time of examination</th>
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<td>2 weeks after nephrectomy</td>
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<td>8 weeks after nephrectomy</td>
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E. Surgical renal cases (Estimation of the separate function)—Table VIII.

Passing now to the record of my observations in cases of surgical renal disease, and to the estimation of the separate function of the kidneys, I would point out that certain difficulties have to be encountered at the outset.

Firstly, it is well recognised that the kidneys do not even in health work simultaneously with the same energy and, moreover, the function of each varies at different times of the day. Nevertheless, when the total excretion of each kidney is estimated over a period of ten or twelve hours, it is found that the work done by each is about the same. Then Albarran (38) has pointed out that though in the course of 10 or 12 hours, both kidneys do practically the same amount of work, yet an observation lasting only 15 minutes might record a difference in their separate activities amounting to 30 per cent, decreasing to 10 per cent when the observations are made for one hour. The estimation of the absolute function of each kidney is, therefore, practically impossible as patients cannot tolerate the presence of an ureteral catheter for more than an hour or two; one has to be content with a determination of the relative functional activity of each organ.

In considering the cases I have investigated, it is noticeable that in many a subnormal activity of a kidney is recorded where at least a normal excretion might have reasonably been expected. This discrepancy may be attributed to one of two factors: (1) Exocathetral leakage. (2) A reflex temporary inhibition of excretion due to the presence of catheters in the
ureters. It is a well known fact that the passage of a ureteric catheter affects the excretion of a kidney causing mostly oliguria but occasionally polyuria. According to Thomson Walker (38) it is the quantity of water excreted that is principally affected by such mechanical procedure, the excretion of the other urinary constituents being but little altered. Such being the case it would appear that provided the collection of urine is complete the 'phthalein test may usefully be employed in determining the functional activity of a kidney. Where, however, urine leaks down the ureter around and outside the catheter, the 'phthalein test becomes of less value. Other tests, such as the estimation of urea, creatinin and diastase activity, giving more accurate and reliable results. For the above reason, I have, in investigating the cases recorded in Table VIII by the 'phthalein method, made collateral observations with regard to the excretion of urea and creatinin and the degree of diastase activity.

The diastase test is not always a reliable index of relative functional capacity (as may be seen in cases 46 and 49), but is of much value in many cases inasmuch as it is not readily affected by dilution: moreover, it is applicable in those cases where only a small amount of urine is obtained (Case 50).

The technique I have adopted in estimating the separate renal function by the 'phthalein test closely follows that made use of in determining the total function. Observations have been made on 15 different patients in association with ureteral catheterisation. The ureters are catheterised: a sufficient amount of urine is collected for ordinary analysis; 1 c.c. of the 'phthalein solution is then injected and the urine is collected and treated exactly as in the test for determining total function.

As a rule the patient is given water to drink immediately after the ureters are catheterised. This induces a free flow of urine. If the urine passed was stained with blood, this was removed by boiling with subsequent filtration.

If it is found impossible to catheterise the ureters, chromocystoscopy
was employed. After the injection of the phthalein, the bladder is filled with a 1 per cent soda solution and the excretion of the kidneys observed, as with the indigo-carmine test. The phthalein test has this advantage over the latter, that the quantitative estimation of phthalein excretion can be combined with the chromocystoscopic observations.

With reference to the thirteen cases recorded in Table VIII it may be said that in the majority the phthalein test afforded valuable information. In only a few instances (Cases 50, 51, 55, 56) did the test fail.
### TABLE

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<th>Case</th>
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<th>Remarks</th>
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<td>Straw</td>
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<td>Albumin</td>
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<td>+</td>
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<td>Sediment</td>
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<td>pus cells</td>
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| I. hr. | 27.00 | 28.00 |
| II. hr. | 13.00 | 10.00 |
| Total | 40.00 | 38.00 |
| III. hr. | 5.00 | 7.00 |
| IV. hr. | 3.00 | 2.00 |

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### VIII.
(Catheterisation of the ureters)

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<th>Date</th>
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<th>Result</th>
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</tbody>
</table>
THE PHENOL-SULPHONE-PHTHALEIN INDEX.

(Phthalein Index)

It has been mentioned that in normal renal cases the amount of 'phthalein excreted in the first hour is at least equal to twice the amount excreted in the second, the total amount excreted in the two hours being equal to about 78 per cent; but a study of different normal and abnormal renal conditions makes it appear that in determining renal function by means of the 'phthalein test, importance must be attached not only to the absolute quantity excreted but to the rapidity of excretion. This may be illustrated by considering two hypothetical cases of abnormal excretion.

In case a

Amount excreted in 1st hour = 39%  
"    "  2nd " = 39%  \[\text{Total} = 78\%\]

In case b

Amount excreted in 1st hour = 25%  
"    "  2nd " = 53%  \[\text{Total} = 78\%\]

In both these cases the amount excreted in two hours is the same; but in the second case elimination proceeds much more slowly and is suggestive of some greater impairment of function.

It seems, therefore, desirable to express the result of the test in some form which will take both factors (viz, the amount excreted and the rapidity of elimination) into consideration.

Soundness of renal function indicated by the 'phthalein test may be said to vary directly as the amount excreted in the first hour and the total in two hours, and inversely as the amount excreted in the second hour. This may be expressed as follows:

\[F = \frac{P_1 \times P_{III}}{P_{II}}\]

Where \[F = \text{renal function}\]

\[P_1 = \text{'Phthalein percentage excreted during the 1st hour,}\]
PII = 'Phthalein percentage excreted during the 2nd hour
and PIII = " " " " the two hours

Applying the formula to the normal renal cases which are found in Table I (normal kidneys) and averaging the results which are there tabulated:

- P_I is found to have a value of 56
- P_{II} " " " 22
- and P_{III} " " " 78

F = \frac{56 \times 78}{22} = 198 or roughly 200

The figure 200 may, therefore, be referred to as the "normal 'phthalein index."

For convenience the number 100 may be substituted for 200.

Thus the 'Phthalein Index = \frac{1}{2} \times \frac{P_I \times P_{III}}{P_{II}} = \frac{P_I \times P_{III}}{2P_{II}}

Applying this formula to each individual case found in the table of normal cases (Table I) the normal index is found to lie between the figures 58 and 138. An index much below 58 is very suggestive of impaired renal function, as may be seen in the Tables which record the index in cases of disease.

CONCLUSIONS.

1. As far as the total or combined function of the kidneys is concerned, I believe, from my study of different normal as well as pathological renal cases, that the claims of Rowntree and Geraphty can be substantiated.
2. The special advantage of the test seems to exist in the simplicity of its technique and the accuracy of the results, factors which make this test far superior to any other methods.
3. In interpreting the findings obtained by the test, importance must be attached not only to the absolute amount excreted, but to the rapidity of the elimination. The two combined factors can be expressed more
accurately in terms of the 'phthalein index as has been proposed.

4. In estimating the separate function of each kidney, the 'phthalein test is for reasons stated of minor value and cannot replace other tests such as the diastase, urea and creatinine estimations.

But in cases where neither inhibition nor exocathetal leakage are present, the test will furnish in itself all the information desirable in regard to the relative as the absolute functional activity of each kidney.

5. The results of the test can be expressed numerically and therefore reveal the degree of the renal function.

6. From the collateral investigations which I have made it may be said that the determination of the daily output of urea and creatinin and the estimation of the diastatic power of the urine furnish no more information with regard to the total renal function than can be obtained from the 'phthalein test. The results of the methods of investigation in nearly all cases confirm those obtained by the use of phenol-sulphone-phthalein.

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