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KIDNEY FUNCTION TESTS

SENIOR THESIS

presented by

WERNER W. MALL

to

THE UNIVERSITY OF NEBRASKA
The kidneys are situated in the posterior part of the abdomen, one on either side of the vertebral column, behind the peritoneum, and surrounded by a mass of fat and loose areolar tissue. The precise level of the kidney in the abdominal cavity varies considerably with the various individuals. Generally their upper extremities are on a level with the upper border of the twelfth thoracic vertebra, their lower extremities on a level with the third lumbar. Usually there is a difference in the level of the two kidneys, the right being, as a rule, slightly lower than the left. The kidneys are not held in place by any distinct ligaments, or special folds of peritoneum, but by a sheath of fibrous tissue continuous with the subperitoneal fascia, named the renal fascia. Posteriorly it extends medialward behind the kidney and blends with the fascia on the Quadratus lumborum and Psoas major and through this is attached to the vertebral column. Above the suprarenal gland the renal fascia unites with the fascia of the diaphragm, while below it is gradually lost in the subperitoneal fascia of the iliac fossa. The kidneys are thus held in position partly through the attachment of the renal fascia and partly by the apposition of the neighboring viscera, or in other words by the pressure and counter-pressure exerted upon them by the neighboring structures.

Embryologically they arise from the mesoderm of the intermediate cell mass (nephrotome), which unites the primitive segments with the lateral layers of somatic and splanchnic mesoderm. In the course of development these anlagen bulge into the coelum as paired longitudinal ridges, termed the urogenital folds. The urogenital fold is the anlage of first the pronephros then the mesonephros, and the permanent kidney is a new organ the metanephros which develop successively, one caused of the other. The essential parts of the
permanent kidney are the renal corpuscles (glomerule with Bowman's capsules), secretory tubules and collecting tubules. The uriniferous tubules are made up of glomerule and capsule which leads into the proximal convoluted tubule into the descending limb of Henle's loop, into the ascending limb, into the distal convoluted tubule, into the collecting tubule, into the papillary duct and into the calix. The action of these different portions is not definitely agreed upon. However the glomerulus is probably fitted histologically for the passage of water and the physical filtration or osmosis of salts from the blood, perhaps under pressure. The cuboidal cells probably perform some further physiological secretion. The large granular cells of the proximal convoluted tubules probably add secretions to the fluid as it passes through the lumen—possibly urea. The cells of the distal convoluted tubules are lower and less granular and may serve to reabsorb some of the immense amount of fluid necessary to carry the salts and other soluble materials through the glomerular wall. The collecting tubules presumably act merely as ducts.

At present there are two theories6-7 of the normal physiology of the kidney in renal secretion. Ludwig's theory maintains that urinary secretion is a simple process of filtration with the glomerulus acting as the filter eliminating from the blood not merely the water but also the solid constituents of the urine, namely, the inorganic salts, and specific elements—urea, etc. He assumes that absorption of water and varying amounts of the other constituents takes place in the passage of the glomerular filtrate through the uriniferous tubules. This theory has in recent years been modified in that his adherents claim now that the absorption taking place in the convoluted tubules is selective in character, so that the theory as now held is not based upon the purely mechanical process of filtration and diffusion. Cushney has recently modified Ludwig's theory and removed some of the objections to it by emphasizing the importance of selective
absorption in the tubules, the final composition of the urine being determined by selective absorption. At present Cushney's explanation is generally accepted. So that it has been more generally accepted that the first act in kidney secretion is the filtration of the liquid part of the blood through the glomeruli into the renal tubule. The filtrate contains in solution all the soluble bodies that are present in the blood so that the glomeruli merely seem to separate the blood corpuscles and colloidal protein from the liquid part. At this stage the parts of the tubules immediately connected with the glomeruli contain a liquid which passes down the tubule is selectively reabsorbed so that the solution becomes more concentrated.

It is our purpose to determine by various kidney-function tests the amount of interference with this mechanism in various pathological conditions.

In the last several decades much work has been done in determining the amount of function of the kidneys in various pathological conditions. The study of the functional behavior of the kidneys by tests has been of great assistance not only to the urologist but to the general surgeon and gynecologist. Prior to their regular use suburemic and uremic conditions were not recognizable before operation and patients frequently succumbed to the surgical intervention; passing into a state of profound uremia with oliguria and anuria. This naturally led to research work for determining the kidney function for the determination of the prognosis both medically and for surgical or non-surgical indications. One of our chief concerns in the consideration of the pathological lesions of the kidney is the renal function, or the ability of the kidneys to carry out satisfactorily the duties imposed upon them by the bodily metabolism. The reason that congestive, toxic and degenerative changes as evidenced by the presence of albumin and casts in the urine, are of interest, is largely because of the lessened kidney function which they bring
out, indicating the potential danger of uremia and death. It is re-
markable how patients may adapt themselves to poor renal function so
that clinically they seem quite normal, whereas often even the slight-
est infection may be a terminal and a fatal one, even without an
operative trauma. Hence it is a lamented fact that tests of renal
efficiency are relatively gross; giving results which do not differ
from the normal until the damage is extensive, and involves from
two thirds to three fourths of the total renal tissue. Yet even
so gross a test has become invaluable to the clinician in safeguarding
the patient against potential uremia. It must, however, be remembered
that renal function tests, like other laboratory tests, should only
be regarded as an extension or an aid to the clinical examination.
If the urine is free from protein, investigations of kidney efficiency
are unnecessary. Proteinuria having been detected, an examination
of the centrifugalized urinary deposit should invariably be made.
If there are no cells, no casts, and nothing abnormal in the deposit
it may be of no significance. If the deposit is abnormal the kidneys
should not be regarded as healthy until subsequent careful and repeated
observations have justified such a conclusion. The simple urinalysis
is the oldest and most universally applied of all renal function tests. 8
Carefully done it gives much important data as to kidney function and
is a determining factor for further functional tests. One can hardly
make a dependable diagnosis of nephritis based on findings of albumin-
uria and casts alone, as there are too many complicating conditions
which may give a transient proteinuria without any definite kidney dam-
age such as traces of albumin during pregnancy, fevers, infections,
exercise, etc. Hence the necessity of further determinations of
the amount of kidney function present.

Many tests have been brought forward only to be again discarded
because of their failure to detect kidney damage. I wish here only
to discuss those tests which are apparently dependable. These are:

1. The Mosenthal, with its variations.
2. Phenolsulphphthalein test.
3. The Indigo-carmine test.
5. Urea-nitrogen.
6. Uric acid.
7. Creatinine.

Other tests as the phloridzin, methylene blue, cryoscopy and electrical conductivity, roseaniline, sodium and potassium iodide, lactose test and many others have been largely placed in the discard.

A test widely approved is the Mosenthal test. Hedinger and Schlayer of Germany\textsuperscript{13} were the first to use this test and Mosenthal modified the test in America and many small variations have been made since by Christian, Foster\textsuperscript{14}, Lashmet & Newberg and many others. As originally described it involved the use of a definite "high protein diet". Later a normal diet was accepted and found not to vary the value of the test, in fact every author has a different diet resume' depending upon the institution. The patient is placed on a definite diet of food and water so that the same amounts and kinds of foods are presented to the kidney in a unit of time. Some\textsuperscript{18} begin the collections of urine at 8:00 o'clock A. M. the same mornings, others place them on a definite diet for several days before collecting the specimens. Specimens are collected every two hours 8:00 A. M., 10:00 A. M., 12:00 Noon, 2:00, 4:00, 7:00, and 10:00 P. M. and at 8:00 the following morning. The specific gravity of each sample is taken. As normals, he gives 1.020 (or 1.018 with the high protein diet) or over in any specimen, as a maximal specific gravity, the extreme values of the different samples to show a variation of 0.009 or more, and a night urine sample of 750 cc. or less. A normal specific gravity indicates that the kidney can concentrate the urine.
satisfactorily. A low, fixed specific gravity is a danger signal of kidney impairment. By fixed specific gravity is meant a variation between 0.009. F. H. Lashmet, M. D. and L. H. Newburgh M. D. of Ann Arbor, Mich. also have a table which they worked out with which they make correction for the albuminuria when it exists. They have found that since specific gravity is dependent on the amount of material in solution and since albumin, when present in the urine, is in solution, it will raise the specific gravity in proportion to its concentration. Albumin is not part of the normal waste, hence it is necessary to discount its effect on the specific gravity that is being used to measure the ability of the kidneys to remove waste. This chart was worked out with egg albumin and shows that the effect of less than .5 per cent of albumin may be neglected but a two per cent solution of albumin will raise the specific gravity more than 7.

M. D. Bell, M. D. of Dallas, Texas has a very simple modification.

"The patient eats three normal meals at 8:00 A. M., 12:00 Noon, and at 5:00 P. M. The patient is required to drink at least one-half pint of fluid at each meal and none between meals. The urine is voided at 8:00 P. M. and discarded. Specimens of urine are collected and saved separately, passed at 10:00 A. M. 12:00 Noon, 2:00 P. M., 6:00 P. M. and 8:00 P. M. and all of the urine passed at night, including a specimen passed at 8:00 A. M. the following day. The quantity of day urine should be at least three times the quantity of the night urine and preferably should be five times that quantity. The night urine should have a specific gravity of at least 1.018. Some of the day specimens should be at least 1.020 specific gravity, and the specific gravity of the day specimens should vary as much as nine points. When the urine does not meet these requirements, the kidneys are not functioning properly at the time of the test, and the more nearly the specific gravity is fixed and the more nearly the quantity of the night urine equals the quantity of the day urine, the more is
the function deranged."

The specific gravity test of dilution and concentration was first popularized by Volhard. His procedure consisted in giving the patient 1,500 cc. of water to drink within three quarters of an hour in the early morning, and then nothing but a dry diet for the rest of the day. Following the ingestion of the water, the specific gravity of the urine drops below 1.002, and the amount of water taken is eliminated in about four hours. Later in the day, the specific gravity mounts, passing 1.025 late in the afternoon.

The phenolsulphonephthalein test is a test for determining the elimination of a dye in a definite time, giving a definite dosage of one cc. of a solution of its monosodium salt of the strength of 6 mg. per cc. This test was originated by Rountree and Geraghty in 1910. The patient drinks two glasses of water and empties the bladder. Then exactly one cc. of phenolsulphonephthalein is injected intramuscularly. Ten minutes is allowed for the dye to be absorbed. In exactly one hour and ten minutes after the injection, all of the urine is passed and saved; at one hour from this time the bladder is again emptied and the complete specimen is saved. Each of these specimens is alkalinized and brought up to a 1000 cc. quantity. The quantity of the dye is then determined by color comparison with the alkalinized standard. The normal kidneys will excrete from 50 to 60 per cent in the first hour and 20 to 30 per cent in the second hour, making a total from 70 to 90 percent excreted in the two hour period.

Recently Shaw, of the Brady Urologic Institute, has shown that the curve of phenolsulphonephthalein excretions gives more reliable information than the two hour test. This has been adequately confirmed by others. In normal individuals the kidney response to the injected dye is quick, and the maximum excretion occurs in the first 15 minutes, the quantity being from 40 to 45 per cent. In the second 15 minutes the excretion drops to from 17 to 22 per cent, and in the eighth
period less than one per cent is excreted. Hence there is a quick response to the load of dye in a normal kidney while in a damaged kidney a greater response is registered in the second 15 minutes or later. The patients with delayed excretion, even though the quantity excreted during the two hour period is normal, do not withstand the shock of urologic surgery as well as those with the quick response.

A test more extensively used in surgical work is the indigocarmine test. From 0.08 to 0.16 g. of the dye is injected intramuscularly. Then either the combined urine or the segregated urines (obtained by ureteric catheterization) are then examined. The points to be noted are the time elapsing between injection and the first appearance of the dye, the time of maximum color, and the time required for complete excretion. Normally the appearance of color occurs in 15-20 minutes and is considered pathological if this time is exceeded. The maximum color appears in about 45 minutes and is considered pathological if the time exceeds one hour. Excretion should be completed in fourteen hours and is considered pathological above fourteen hours. When used this test is almost invariably carried out by the surgeon himself.

Other tests which are much more complicated and require an experienced technician and elaborate equipment are the non-protein nitrogen, urea nitrogen, uric acid and creatinine tests of the blood. Of the nitrogenous constituents the kidney excretes creatinine most readily, urea next, and uric acid with the most difficulty. Hence an impairment of function usually results in first the retention of uric acid, then urea, and finally creatinine. Urea, 15-40 mg. per 100 cc. is the chief constituent of the non-protein nitrogen and hence its retention affects the non-protein nitrogen to the greatest extent. The non-protein nitrogen however increases only when about 60% of the functional capacity of the kidney has been lost, this in consequence
means bilateral involvement. From 20 to 50 mg. of non-protein nitrogen may be taken as normal but any amount above 50 mg. may safely be considered evidence of retention. When the creatinine is above 2 mg. per 100 cc. there is serious functional derangement of the kidneys. If it reaches 5 mg. per 100 cc. the prognosis is almost always fatal. Uric acid may be considered pathological when it goes above 4 mgm. Two or three mg. per 100 cc. normally being present. The uric acid test is however of practically no value as many conditions may vary its value. Most hospitals use the non-protein nitrogen or urea-nitrogen test and if it is above normal a creatinine test is made for prognosis. Blood urea if done by the urease method is very reliable if done by an experienced technician.

Work was done in the Mayo laboratories on a simple index of renal insufficiency by the salivary urea and the mercury combining power of saliva. They found that the concentration of urea in the saliva increases approximately the same relationship as the blood urea concentration, although slightly lower figures are generally obtained. They made a study of the mercury combining power of saliva and the estimations of blood urea. They titrated saliva with mercuric chloride until an end point was reached with saturated sodium carbonate on a porcelain plate and expressed this in cubic centimeters (5 per cent bichlorid of mercury for each 100 cc. of saliva) and called it the salivary urea index. The mercury combining power of saliva being normally between 30 and 50 (cc. bichlorid of mercury) for each 100 cc. saliva and this increases in definite relationship to the increase of blood urea nitrogen. Hence the mercury combining power of saliva may be utilized as a urea index. Dr. S. D. Rhind of Wellington, New Zealand describes a very simple technique which may be done by any practicing physician. A 5% solution of mercuric chloride is placed in a burette and titrated into 5 cc.
of saliva, a drop of saturated solution of sodium carbonate being used on a porcelain dish as an indicator. The end point is indicated by a reddish-brown tinge in the carbonate solution. It is found that in normal subjects twenty to fifty cubic centimeters of the mercuric chloride solution is required to combine with 100 cc. of saliva and this corresponds to the normal 20 to 40 mgm. of blood urea. The values will not always agree absolutely, but will run parallel."

Dr. Khind carried out a series of these tests at the Wellington hospital and although he commenced the investigation with considerable doubt he was amazed at the parallelism of the blood urea and the salivary urea.

The urea concentration test was devised by MacLean and de Wesselow for forcing the kidneys to concentrate urea by flooding the blood with urea, and by withholding fluids for 8 to 12 hours the bladder is emptied and a definite dose of urea of 15 gms. is given, or 1 gm. per 10 pounds of body weight. Then collect three hourly specimens and determine the percentage of urea in the three specimens by the hypobromite method. Volumes are also measured to detect excessive diuresis. The volume of urine should not exceed 120 cc. in the first hour of 100 cc. in the second and third hour. If the volume does exceed this, a low concentration is not necessarily indicative of deficient renal function and the test should be repeated. If the urea concentration be good in spite of excessive diuresis there is no need to repeat the test. The information required is the maximum concentration of urea which may occur in any of the three hours. Normally the maximum concentration exceeds 2.5 to 3 or more per cent. Figures between 2 and 2.5 per cent. are on the boundary line and a blood urea or any other tests should be made. Figures below 2 per cent. generally indicate renal inadequacy providing the test has been properly executed. The blood urea test is often used in conjunction
with the urea concentration test in which blood, for the determination of blood urea, is taken after the administration of dye. One specimen just before the administration, one two hours later and fourteen hours after the administration the third specimen is taken. The blood urea in the second specimen indicates adequate absorption of urea. The elevation of blood urea nitrogen persisting above the rest level (taken as fourteen hours after the ingestion of urea) is used as the basis of interpretation of the test. Variations up to 2 mg. of blood urea nitrogen above the control level is considered as within normal limits, providing the output of urine is not excessive. A urine volume of over 750 cc. for the fourteen hours is also considered abnormal. 

Dr. S. Edward King of New York ran a series of tests on patients with definitely impaired renal function and found that:

"The blood urea, two hours following the ingestion of urea, was definitely higher than normal. The average elevations in terms of blood urea nitrogen was 15.9 compared with a normal average of 10.5. Individual elevations of over 18 mg. were obtained. After fourteen hours, there remained residual elevation of 10.3 mg. above the control method. Consequently on the average, less than one third of the urea given had disappeared from the blood. In about half of these cases, a marked polyuria, over 750 cc., was present for the fourteen hour period in addition to the abnormal curve. He found in a series of normal cases that there occurred a characteristic normal curve of blood urea which returned to a normal level fourteen hours after the ingestion if urea, while a deviation from the normal occurred even in the early stages of renal impairment, which became more marked with more severe cases. He also found that early degrees of renal impairment were frequently indicated by marked fourteen hour polyuria (750 cc.) although the blood curve remained normal. That urea retention is characteristic of renal failure leading to clinical uremia has long been recognized. Van Slyke, McIntosh, Möeller, Hannon, and Johnson have presented data showing that the urea ex-
creting ability of the kidneys was, in fact, the most sensitive indicator of the state of the renal function of several which they tested, including blood urea, and blood creatinine concentrations, and phenolsulfonephthalein excretion. As a measure of the urea excreting power of the kidneys it has been recognized since the work of Ambard (914) and F. C. McLean (1915-1917) that the most exact information requires comparison of both blood urea concentration and urea excretion in the urine. From the work of Moller, McIntosh, and Van Slyke (1928) it appears that the simplest and most satisfactory way to express the relationship between these two factors is by means of the "blood urea clearance" by which it meant the cubic centimeters of blood per minute cleared of urea by renal excretion. For urine volumes below 2 cc. per minute, as shown previously by Austin, Stillman, and Van Slyke (1921) the blood urea clearance decreases with diminishing urine volume. Diminishing the volume to one fourth was found to lower the clearance to one half: hence the clearance varies in proportion to the square root of the urine volume. Making allowance for this influence of urine volume, the blood urea clearance, from determinations with any urine volume below 2 cc. per minute, is estimated for the standard condition that urine volume output is 1 cc. per minute the formula (Moller, McIntosh and Van Slyke 1928) used being:

\[
\text{Standard blood urea clearance} = \frac{U}{B} \sqrt{V}
\]

U. = concentration of urine.
B. = concentration in the blood
V. = volume output of urine in cc. per minute.

Van Slyke, McIntosh, Moller, Hannon, and Johnson (1930) found that the urea clearance test fell below 40% of normal renal function in many cases when the PSP excretion, blood creatinine and blood urea considered without its relation to urea excretion, were still within the range of normal variation. The average normal clearance in adults
is 54 cc. per minute. For urine volumes above 2 cc. per minute
Austin, Stillmen, and Van Slyke (1921) showed that the clearance is
independent of the volume. With urine volumes over 2 cc. per minute
the clearance is calculated simply as $\frac{UV}{B}$. The average value of this
"maximum clearance" for adults is 75 cc. of blood cleared of urea
per minute. They found that in hemorrhagic and degenerative nephritis
one may interpret the blood urea clearance as a measure of the pro-
portions of the glomerular tissue still functioning. While in ter-
minal arteriosclerotic nephritis clearance values which are a small
fraction of normal have been found with a large proportion of glomerule
still intact. Hence it appears probable that in arteriosclerotic nep-
hritis the fall in blood urea clearance is proportional to the de-
crease in renal blood flow rather than to the glomerular destruction.
Sufficient time has not yet elapsed to prove the superiority of
this method for the determination of urea excretion. Recently the urea
clearance test has been worked out with very excellent results by Van
Slyke, McIntosh, Moller, Hannon, Johnson mentioned above also by Edgar
Stillman, rich, L. Leiter, MacKay, N. S. Moore, Christopher and many
others, who prove it to be the most delicate test yet discovered.
In fact this test is at the present time looked upon as the means of
definite progress in research on the detection of incipient nephritic
conditions. Definite progress in the detection of incipient kidney
conditions will, in all probability, be made with the mastery of
this technique. At the present time it seems to promise more than
any test has accomplished in the past.

A few years ago, before the urea-clearance test became known,
the Mosenthal test was considered the most delicate. This test prob-
ably gives the greatest returns for the effort invested. It is easy
to perform and requires a minimum of laboratory apparatus. Addis
has pointed out that when it is desired to measure the capacity of an
organ to perform its function it is necessary to arrange the test so
that the organ will be working at its maximal capacity. The Mosenthal provides for a standard waste to be removed by the kidney during a time when it is forced to function at its maximal capacity. The test also provides for the measurement of the total function of the kidneys under such conditions. It therefore apparently affords a better insight as to the functional ability of the kidneys before either the phenolsulphonylphthalein test or the estimation of the blood non-protein nitrogen. MacLean records excellent results with the urea concentration tests in a series of more than 10,000 cases. Kabinowitch likewise reports good results. Howen, in a comparison of various renal function tests, concluded that the urea test was more delicate than the P. S. P test and found it correspondingly better with the day night urine volume ratio and specific gravity which Christian & O'Hara consider the most delicate test of all, than did the P. S. P. test or blood urea nitrogen. In spite of these favorable reports the test has not been generally adapted in America. The P. S. P. seems still to be the most popular in America even though it is shown by many authors not to be as delicate as the specific gravity test of Mosenthal.

M. M. Wintrobe, New Orleans, J. L. & C. Med. (14) made a study of the comparison of urea concentration and the P. S. P. tests in 49 healthy individuals, and the value of these tests, as well as of urinalysis and blood chemistry determinations, in 56 patients and found that the power of concentration appears to be a definite function of the kidney and one which is early involved in the damage produced by nephritis. Thus, most observers agree that the earliest sign of kidney damage as shown by laboratory tests is an increase in the volume of the night urine and a decrease in its specific gravity, or, in other words, a decrease in its concentration. MacLean's test measures the concentrating power of the kidney in response to a definite stimulus by a method which is even more simple than that necessary
for the carrying out of the various water concentration tests, and in both theory and practice is a valuable test of renal function. Where there is a congestive cardiac failure, the urea concentration test probably gives a more correct conception of the functional state of the kidneys than does the P. S. P. test.

John H. Musser, New Orleans and Arthur W. Phillips of Philadelphia carried out a series of tests in the aged and found that in outpatient work it is impossible to rely upon any single test of kidney function; one may be abnormal, with the others normal. They found that by comparison of blood pressure, blood urea nitrogen, phenolsulphonephthalein, and urine tests in the aged that the P. S. P. test is the one most likely to show abnormalities, the blood pressure the least. In an individual past 70, 88% will give evidence of renal involvement based upon one or another of the criteria of elevation of blood pressure, a lowering of phthalein output, an increase in the blood nitrogenous waste products and the presence of albumin and casts in the urine. The P. S. P. or indigo-carmine tests have the advantage of determining the function of each kidney separately, thus obtaining a rough comparison between the efficiency of each of the two kidneys. However, tests of kidney function which depend on the retention or excretion of a single substance, such as urea or a dye, are open to the objection that there is no evidence that the kidneys excrete other waste products in the same proportion as the substances examined.

Arthur M. Fishberg of New York states that; "Since impairment of renal function consists in a diminution in the concentrating capacity of the kidney, the most logical and direct tests of renal function are those which measure the concentration of one or more urinary constituents. The most useful variety of concentration test, requiring no laboratory facilities, is the specific gravity test, for which the technique is simple."

B. A. Thomas of Pennsylvania thinks the most reliable test is
the Mosenthal test day meal by which, normally, the versatility of the renal function can be demonstrated by:

1. Variability in the specific gravity of the urine of ten or more points;
2. Balance of the intake and output of salt, nitrogen, and fluid;
3. (a) Specific gravity of the night urine of 1.016 or higher;
   (b) Content of nitrogen of over 1%;
   (c) An amount of 400 cc. or less.

This test is invaluable for the determination if incipient nephritis, but is a measure of the lessening of the versatility of the kidney function in relative insufficiency and is of no value in absolute renal insufficiency. It subjects the kidneys to definite stress—the essence of any true physiological test, but, as is the case with the other tests it is subject to interference by certain extra-renal factors. He believes that the dilution and concentration test of Volhard and Fahr offers nothing of advantage over Mosenthal's test.

Tests of kidney function can be broadly divided into the blood biochemical tests of urea nitrogen retention and kidney tests of elimination of endogenous products as urea and exogenous products as indigo-carmine and phenolsulphonephthalein products. It is generally accepted that blood biochemical determinations of nitrogen cannot be accepted without reservations as infallible proof of true nitrogen concentration of the blood and renal insufficiency. Yet blood biochemical tests of nitrogen retention alone or in conjunction with other tests of elimination are of inestimable value in determining the amount of kidney function. The time will probably never come when any one functional kidney test will be found so infallible that reliance should be placed unreservedly upon it to the exclusion of all others. It is a relatively simple thing to get a positive test with practically any method after the pathological condition of the kidney shows definite clinical manifestations. Hence our problem
is the problem of discovering a kidney function test which will uncover an incipient nephritic condition which has relatively no clinical manifestations. To the practicing physician who has few laboratory facilities, the Mosenthal or one of its variations may be easily used and is probably the most delicate test which he can make. A complete urinalysis of course having been done for indication of further kidney function tests. Possibly the next in choice is the phenolsulphosphate test. The salivary index test might also be used. However in a hospital with modern facilities where tests are carried out for delicate diagnosis I would place the tests in this order as to their delicacy in unearthing an incipient nephritis:

1. The urea-clearance test.
2. The Mosenthal test.
3. The Phenolsulphosphate or indigo-carmine test.
4. Non-protein nitrogen
5. Blood urea nitrogen.
6. Creatinine.

With the evidence at hand I believe that given a case of impaired kidney function the urea-clearance test would be a more delicate test than any other. A P. S. P. might be negative while the Mosenthal would be positive, or the non-protein nitrogen be negative and the P. S. P. positive, etc. Each test being a little more delicate than the one listed below it.

Certainly there is no doubt that the sooner that physicians stop assuring patients, suspected of interstitial nephritis, that their kidneys are all right because a single specimen of urine does not contain albumin and cast; or advising another patient that he has Bright's disease, just because albumin or casts were found in a single specimen of urine, and really study every patient suspected of nephritis clinically, by history, by routine urine examination and by functional tests, the sooner will we begin to recognize inter-
stitial nephritis in its incipiency. It is at this time that removal of focal infection and regulation of the life and diet of the patient may arrest the condition, and leave him with adequately compensating kidneys for the rest of his natural life.
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