DETERMINATION OF THE EXTENT AND NATURE OF THE RENAL LESION IN BRIGHT'S DISEASE *

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This year Christian has collected in a text book [1] a summary of the more important facts which have been established as to Bright's disease. He and his collaborators have made careful and extensive investigations with the most recent methods and his critical review of our present position therefore carries great weight. When I had read it I looked up Bright's Medical Cases,[2] published nearly a century ago. The differences were interesting. One of the most striking was the presence in the modern treatise of many tables of figures giving the results of functional tests. There were no figures in the old book. Yet Bright had noted the existence of changes in the volume of urine and in the amount of albumen it contained. He had even in certain cases observed that the amount of urea in the blood was increased, though at the same time there was less than usual in the urine. In another type of case he had noted the existence of lipemia and of a decrease in the protein content of the blood. We are now able to give a quantitative numerical expression to these qualitative observations of Bright's. But this difference is, after all, often only superficial. No one, I imagine, would be more ready than Dr. Christian to admit that our modern exactitude of expression does not necessarily carry with it any greater knowledge than Bright possessed as to the origin and significance of the changes we can now follow so closely.

But there was another and a more fundamental difference between the new and the old. It lay in the attitude taken towards the relation between functure and structure. The modern point of view, and I believe this fairly represents the feeling of those who have had most experience, appears to be that it is illusory to attempt to draw anatomical deductions from our clinical observations and functional tests. Bright would never have subscribed to this opinion. The sub-title of his book is, "illustrating the symptoms and cure of diseases *by a reference to morbid anatomy.*"

It was to anatomy, not to physiology, that he looked for the clue to treatment. He studied functional abnormalities in his patients as aids towards the construction in his mind of a clear picture of the structural defects from which they arose. He believed that as experience accumulated it would be possible for the physician to see through the varying symptomatology and changing functional reactions to the hidden anatomical cause. But as a matter of fact, as experience has accumulated, as methods which supposedly measure the functional capacity of the kidneys have developed, the discrepancy between clinical predictions and post-mortem findings has become more and more apparent.

The recent review I mentioned admits the impossibility of making an anatomical diagnosis. During the last decade there has been a tendency not only to admit this fact, but to set it aside as of no moment. We are now inclined to take the results of functional tests as ends in themselves and not as means towards an anatomical diagnosis. We comfort ourselves with such statements as, "It is more important to know what the kidney can do than to be able to say what it looks like," and so on.

This modern spirit of resignation in failure is due not only to a deeper knowledge of the difficulties of the task Bright set, but in part at least it rests on a satisfaction with our new functional methods. Even if it must be admitted that our results are not always in accord with anatomical findings, we can say that that may after all be due to the inadequacy of histological technique. It is easy to point to special instances where this is certainly true. It is easy for the clinician to believe in his methods and to wait with patience for the anatomy of the future to come into line with his clinical physiology.

There is, of course, plenty of evidence that the present divorce between clinical and pathological findings is in part due to the inadequacy of clinical and not of histological methods. For instance, in circumstances where there is no possibility of any structural abnormality invisible to the microscope, in cases where the renal tissue is entirely normal, we can remove half of that tissue from the body by taking out one kidney, and yet find that the results of the methods now in use will still lie well within the range of normal variation. If our methods cannot tell us when half the renal tissue has been removed, it is clear they are not able to tell us how extensive has been the destruction of tissue in a case of Bright's disease. Yet this is a practical anatomical question which may be of great importance for treatment and prognosis.

It should not be impossible to develop a functional method which would answer this question; for it is axiomatic that functional activity can manifest itself only through and by means of structure. It should be possible to find conditions under which functional activity is limited by structure, so that we could take our functional results as an indirect measure of the amount of secreting tissue present. Since 1913 we have been working at this problem, and as a result of experimental work [3] we have developed a functional method which I believe enables us to make a rough estimate of the amount of actively secreting renal tissue in the living kidney.

The main requirements of such a test became apparent as a result of a study of the factors influencing the degree of variability in the function of the normal kidney. Everyone is familiar with the wide fluctuations in the activity of the kidney, even of the same kidney under apparently identical external conditions. Since the structure is constant, such variations in function must be caused by other than anatomical factors. It was found that no matter how carefully external factors, such as food and water intake, were controlled, there was still a considerable variation in the

* The work on which this paper is based has been aided during the past year by a fund raised by Mr. Wellington Gregg and his friends.

activity of the kidney when measured over short time periods, and that this variation was in part explained by changes in the concentration of urinary constituents in the blood. It was necessary, therefore, to choose some substances whose concentration in the blood could be accurately determined during the period when its rate of excretion was being measured. This substance had also to be one of the so-called "non-threshold" substances, for otherwise changes in the threshold which could not be controlled or measured might influence the results.

We chose urea and studied the factors which induced those variations in the rate of urea excretion which were not to be accounted for by changes in the concentration of urea in the blood. The external requirements of the method were thus determined. But even after the elimination of many disturbing factors, and even though the effect of changes in blood urea concentration had been discounted, there still remained a considerable variability in the rate of urea excretion. It was only when the kidney was put under strain by the administration of large amounts of urea and water that this variability disappeared.

Everyone is familiar with the relative constancy of action of the kidney in terminal cases of chronic Bright's disease, when there is retention of urinary constituents in the blood and very little normal renal tissue left. Normal kidneys show the same constancy when they are given more work than they have ever had to do before, more work than they can at once perform. By giving a large amount of urea by mouth a temporary uremia is produced. Under these conditions all the kidney tissue works at top speed, and the rate of urea excretion is limited only by the amount of actively secreting tissue present.

The details of the test are as follows: The blood urea concentration is first determined in order to find how much urea will have to be given. If, as often happens even in fairly far advanced cases of Bright's disease, there is no increase in the amount of urea in the blood, the patient is given 30 grams of urea, or 20, 15, 10 or 5 grams, depending on the degree of urea retention which may be present. If the urea concentration in the blood is over 75 mgs. per 100 cc., no urea need be given. At 6 a. m. next morning the patient slowly drinks a quart of water in which the required amount of urea has been dissolved, and every hour thereafter drinks two glasses of water. No breakfast may be taken, since protein food has a marked effect on the rate of urea excretion quite apart from its effect on the blood urea concentration. By 9 a. m. the apex of the curve of the raised blood urea concentration is passed and during the next three hours it falls slowly. This is the time during which three accurately timed urine collections are made, and the level of the curve of blood urea concentration determined by analyzing three samples of blood drawn in the middle of each of the three periods over which the rate of urea excretion is measured. From these the rates of urea excretion per hour are calculated and divided by the amounts of urea found in 100 cc. of the blood obtained in the middle of each period. In the same individual under these conditions this ratio remains nearly constant.

In different normal individuals there are constant individual differences. The average ratio for normal individuals is approximately 50—i. e., there is 50 times more urea excreted in one hour's urine than is found in 100 cc. of blood removed while the urea is being excreted. This is independent of the actual level of blood urea concentration. We have a large number of observations of normal individuals, but we are still collecting further data, and it will be some time before it will be possible to determine the probable error of the ratio in normals. We have a series of observations on patients on whom the blood urea concentration and the phenolsulphonephthalein test gave normal results, who yet gave ratios below the lower limit of normal variation. In such cases we believe that the degree of depression of the ratio measures in an approximate manner the degree of destruction of the actively secreting renal tissue. We believe that from these functional results we are justified in drawing conclusions as to the extent of the pathological process in the kidney.

There is another anatomical question often of the utmost clinical importance which is for the most part neglected by the clinician. Prognosis depends not only on the extent but also on the nature of the renal lesion. Inflammatory conditions in which the glomeruli are involved are the most grave, since this type of lesion sometimes progresses until almost no normal renal tissue is left, and even if it heals, always leaves scars. The degenerations are relatively seldom progressive, and on account of the great capacity of the tubules for regeneration, often end in a complete restitution of the secreting tissue. The atrophic lesions, though progressive, are usually so slow that prognosis is good so far as the kidney is concerned. But in making these distinctions, clinical symptomatology is a very poor guide and functional results are of little value. The only method available is the direct one of looking in the urine for anatomical evidences of renal inflammation, degeneration or atrophy. We have, therefore, for some years carried on a systematic investigation of the urinary sediment in cases of Bright's disease. It was soon found that a certain uniformity in the conditions under which the urine was collected was necessary, and since we observed a disappearance of casts in serial observations on cases in whom diuresis was induced by water drinking, we adopted the following plan under which a urine of high concentration is obtained in all except terminal cases of chronic Bright's disease:

The patient is given a wide-necked cylindrical bottle with written instructions to the effect that from breakfast time until next morning, when the urine is collected, no fluids of any sort are to be taken, that at a certain hour in the evening urine is to be voided and discarded, and that next morning the whole twelve hours' night urine is to be

passed directly into the bottle. The urine so collected is allowed to sediment for an hour, and 30 cc. are then carefully pipetted from the bottom of the bottle, special care being taken in so doing that the pipette passes all round the rim and over the whole surface of the bottom of the vessel. The sediment thus collected is centrifuged, the centrifuge inverted at an angle of about 20 degrees so that all of the urine drains off, and the deposit at the tip is removed by a capillary pipette to a slide, while the inverted position of the centrifuge tube is still maintained. If this is not done the urine hanging on the edge of the tube will run back and dilute the centrifuged deposit. In cases where we know that a large number of casts are to be expected we mix up the whole twelve hours' urine and centrifuge in a graduated tube. All but 0.5 or 0.25 cc. of urine is then pipetted off, leaving the deposit undisturbed. After thorough mixing, a drop is placed on a white blood cell counter and from the count the total number of casts in the twelve-hour specimen is calculated. In cases where there are only a few casts they can be counted directly on a slide. In all cases where a sufficient number can be found a differential count of the casts is made. Note is also made of the number of red blood cells, leucocytes, and epithelial cells.

This method has been especially helpful in the diagnosis of glomerular nephritis, the only clinically important form of Bright's disease in which an acute inflammatory lesion is primary. During the early stages, as might be expected, there are large numbers of leucocytes and red blood cells in the urine, but in this there is nothing which can be taken as indicative of glomerular inflammation, since blood and pus are common to an acute inflammatory lesion anywhere in the urinary tract. But there is one form of cast, the blood cast, which I believe is found only in glomerular nephritis. I have not been able to find anywhere a description of the many forms and appearances which blood casts may take. The erythrocytes often become so agglutinated that they are no longer recognizable and only the deep yellow or brownish color remains to indicate the original composition of the cast. It requires some experience to be able to distinguish this form of blood cast from the granular cast, originally epithelial, which is yellow because of the presence of a pigment which appears to be analagous to the pigment found in the cardiac muscle cells in "brown atrophy" of the heart.

But it is especially in the later stages of glomerular nephritis that the finding of blood casts appears to be of special diagnostic importance. We have a number of cases under observation in whose urine a few, sometimes only one or two, blood casts are almost constantly found. In some of these cases there has been a preceding acute glomerular nephritis with general anasarca, but in most of them there is not even a history suggestive of such a condition. If these kidneys could be examined microscopically I believe it would be found that a few glomeruli would show evidence of an active inflammatory lesion. Some of these glomeruli will in time be so damaged as to become functionless and their tubules will degenerate and be replaced by fibrous tissue. As this process extends to other renal elements there will be a slow disintegration of the secreting tissue.

In a few cases which we have been able to follow for some years it would appear that the progress of the pathological process is so slow that the condition may never produce a lesion so extensive as to be of clinical importance. But it seems not improbable that it is these commonly unrecognized cases of focal glomerular nephritis which may be seen for the first time when complete renal insufficiency is impending and in whose small cirrhotic kidneys the pathologist finds evidence that the primary lesion has been a glomerular inflammation.

The cases of Bright's disease in which a degeneration of the parenchyma of the kidney is the primary lesion give evidence of damage to the tubular epithalium in the form of epithalial casts and of the coarsely granular casts which are derived from the disintegration of the epithalial cells. In certain forms, also, the sediment shows many hyeline and epithelial casts with fat droplets. Some of these droplets are doubly refractile. They are not pathognomonic of a fatty degeneration of the renal cells, since we have confirmed Gross's statement [4] that they may be produced in any case of Bright's disease by feeding cholesterol. But this finding is none the less of diagnostic importance, since it is found in a group of cases which form a distinct subdivision of Bright's disease, with its own peculiarities of prognosis and its own special requirement as regards treatment.

Although many instances in which a degeneration is the primary lesion recover completely, there are a certain number, larger I believe than is usually supposed, in which the condition progresses

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Is It Chiro-Quack-Tic?—Under this heading Leslie's Weekly, beginning with the issue of January 4, is running a series of articles of incalculable value to the public. These articles, written by Mr. Severance Johnson, an experienced writer, are of the same general character that Samuel Hopkins Adams used in "The Great American Fraud" a great many years ago. Not only physicians but every citizen should read these articles and see what they are really invited to support by their ballots and by their co-operation in this and in other States. Leslie's Weekly is rendering the public a splendid service in the publication of these articles, and physicians above all people should read them and pass their copies along for other people to read.

Arizona, California and Nevada Sections of the American College of Surgeons—The first group meeting of the three States was held in one of the hotels of Los Angeles on February 17 to 18. Stanley Stillman of San Francisco, chairman; Lewis R. Morton of Los Angeles, secretary, and Granville MacGowan of Los Angeles, chairman of the committee on arrangements. One meeting was devoted to questions of hospital betterment. There were two scientific surgical meetings, and one morning was given over to clinical demonstrations in Los Angeles hospitals.

to a stage in which the destruction of secreting tissue is so great that the remaining tissues become insufficient for life. We followed one such case through almost its entire course and found in the end a contracting kidney in which the microscopical findings indicated that a degeneration was the primary lesion, and we have several others under observation in various stages of renal decompensation. In none of these cases have blood casts ever been found.

Kidneys in which there is neither an acute glomerular inflammation nor any pronounced tubular degeneration may suffer a slow and partial atrophy which is associated with an arteriosclerosis of the renal arteries. The urine shows a variable number of hyaline casts with an occasional epithelial or coarsely granular cast and only a trace of albumen. The functional capacity is diminished, but we have never yet found any extreme loss of function. It is still uncertain whether this very slowly progressive lesion ever becomes so extensive as to lead to death in uremia. The evidence from the clinical side will have to come from systematic urinary examinations and repeated determinations of the extent of the lesion. Direct and positive evidence of the possibility of such a development would be given if a gradual failure of functional capacity were shown, combined with the development of the typical urinary sediment found in terminal cases of contracted kidney, and this without the appearance at any time of any indication of acute glomerular inflammation or active tubular degeneration.

In cases bordering on or actually in uremia there are a considerable number in which no evidence of active inflammation or degeneration can be found. Instead there are large numbers of casts which vary widely in size, from those with the usual breadth through all stages up to those which are four or five times broader than ordinary casts. I think it is justifiable to regard such broad casts as direct anatomical proof of the dilatation of the tubules which postmortem examination shows in these kidneys. The casts in such cases have a characteristic appearance. Those which might be called hyaline have not the transparency of the ordinary hyaline cast, but seem to be of a denser material, and there are all grades of transition to the typical waxy cast. The granular casts are more granular than usual. Some are composed of a highly refractile material in which what might be the faint outlines of degenerated epithelial cells or leucocytes can be seen, but more often they have an appearance suggesting a loose aggregation of dark particles which appear quite black under the low power, and have not the sharply defined and regular contour which casts usually possess.

The interpretation of these findings is largely dependent on a comparison of the character of the urinary sediment during life with the nature of the lesion as revealed by a microscopical study of the kidney after death. Our postmortem material is as yet small, so that our conclusions can only be provisional. But there is enough to encourage us in the belief that a careful examination of the urinary sediment will often give very direct evidence as to the nature of the lesion in the kidney.

Even though we were always able to determine with accuracy both the nature and the extent of the renal lesion, we should still be far from a real knowledge of Bright's disease; for in Bright's disease more than the kidney is involved, and in some of its forms, prognosis and treatment depend on an evaluation of the condition of the heart, of the vessels and of the effect of the disease on other organs, as well as on an estimate of the state of the kidneys. But just on account of the complexities of these problems it is important, for purposes of analysis, to consider each of the elements separately, and only in the end to combine them in a composite judgment. The renal lesion is one of these elements, often the most important, and this special problem can only be solved when we are able to answer two questions, the question of the nature of the lesion and the question of its extent. I believe that a thorough and systematic examination of the urinary sediment under controlled conditions gives the most direct evidence as to the nature of the lesion, while its extent must be determined by a measurement of the total functional capacity of the kidneys under conditions designed to call forth the greatest possible amount of work of which they are capable.

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A FALSE RUMOR

This office is amazed to discover that a rumor is prevalent that members of the Indemnity Defense Fund have been assessed $30 a year since the institution of the fund in December, 1916. This is not true. The first assessment on Fund Members will be levied this year. Those who joined it at its inauguration have had the benefit of its protection for five years without assessment of any kind for that period.

Payment of $15 in cash and the execution of a note in the sum of $15 due one year after date entitles any member in good standing to join the fund.