A Clinical Lecture ON THE DIFFERENTIAL DIAGNOSIS IN CASES OF ALBUMINURIA.

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ALBUMINURIA is the term used to denote the passage in the urine of preteid that is coagulable on boiling. More than one substance is included in the word "albumen" in this sense, and there are varying proportions of serum albumen and serum globulin in different cases. So variable may be the relative amounts of these, not only in different diseases, but also in different cases of the same disease and in the same patient at different times, that there is little useful clinical information to be obtained by dealing with the albumen and the globulin separately, at any rate so far as present knowledge goes. Nucleo-proteid or nucleo-albumen comes in quite a different category.

Although a large number of different tests for albumen have been devised and advocated, for clinical purposes there is little need to trouble about more than the two common ones—namely, the acetic acid and boiling, and the cold nitric acid tests. It is true that each of these has fallacies; but the latter are not common to both, and therefore, if there is any doubt in the interpretation of one of the two tests, it can readily be confirmed or otherwise by the other. It is alleged that more delicate tests exist; but there is such a thing as too great delicacy in a clinical method. One does not want to find albumen in minute traces where it does not matter, and it seldom matters until its amount is sufficient to give both the common tests.

THE ACETIC ACID AND BOILING TEST.

A test-tube three parts full of urine—cleared if need be by filtration—is held by its lower end, whilst its upper part is carefully heated to boiling point. It is best not to add any acetic acid before boiling unless the specimen is distinctly alkaline, in which case it may be just acidulated with a drop of acetic acid. After boiling, the tube should be held in a good surface light against a dark background, such as the sleeve of one's coat; any opalescence will be obvious at once, and there may be a dense white cloud. Except in very rare cases of Bence-Jones's albumosuria this cloud will be due to one or more of three things—namely, calcium and magnesium phosphate, calcium carbonate, or coagulated albumen. One, two or more drops of acetic acid solution (B.P.) are now added; if the cloud disappears entirely, quietly, and at once, it was due to earthy phosphates, and no albumen is present; if it disappears entirely but with brisk effervescence, the latter is due to calcium carbonates amongst the phosphates, and no albumen is present; if, on the other hand, the cloud clears up but partially, or remains unaltered, or actually increases and becomes more flocculent, albumen is almost certainly present. There is only one serious fallacy remaining, and that is in regard to nucleo-proteid; this is precipitated by acetic acid, and it is possible for a cloud of phosphates to be cleared up by the latter and yet for a faint cloud of nucleo-proteid to come down in the place of the phosphates in such a way as to suggest that the original cloud was not wholly soluble in the acid, and therefore that albumen is present when it is not. There are three ways of obviating this source of fallacy: the first is to add a single drop of dilute non-fuming nitric acid to the suspicious cloud that remains after the addition of acetic acid; if it is due to albumen, it will persist or even increase, whilst if it is due to nucleo-proteid the nitric acid will disperse it; the second is to perform the cold nitric acid test for albumen as described below—nucleo-proteid will not give a definite localized white ring with it; and thirdly, a control test may be done, acetic acid being added to another specimen of the urine without boiling, and the cloud due to any nucleo-proteid present compared with the cloud in the acidulated and boiled specimen.

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HELLER'S COLD NITRIC ACID TEST.

About 1½ in. of urine is poured into a test-tube, the latter is held much inclined, and colourless nitric acid is allowed to flow gently down the side, until about one-third as much as the urine has been added. The nitric acid is heavier than urine and goes to the bottom; if albumen is present, a white ring forms at the junction of the two fluids. Some prefer to pour the nitric acid into the test-tube first and then to add the urine carefully with a pipette. It is important not to shake the tube or the nitric acid and the urine will mix, and there will be no definite line of junction between them. Fuming nitric acid must be avoided, because the nitrous oxide fumes cause decomposition of the urea, and the resultant bubbles mix the fluids; sometimes there is bubbling even when the nitric acid is colourless, in which case this is due to CO₂ set free from carbonates. The test is very delicate: if any large quantity of albumen is present, the ring appears at once; if there is only a trace, the white ring may not appear for a little, and the tube should be set aside and looked at again in a few minutes. Broadly speaking, it takes three minutes for it to develop when the amount of albumen is 1 part in 30,000. This test is open to more fallacies, however, than the acetic acid and boiling test, so that the nitric acid test should not be trusted to alone, unless it is negative. In concentrated urines it is common to get a dark brown, reddish-brown, or violet-brown ring of colour at the junction. This is nothing to do with albumen; it is generally most marked in cases of indicanuria. White rings, more or less like that due to albumen, may also be due to any of the following:

1. *Resin*.—If the patient is taking copaiba resin, or other similar drug, enough of the resin may be excreted in the urine to form a diffuse white cloud above the nitric acid. This source of fallacy is best avoided by bearing it in mind and checking the nitric acid test by the heat test; this latter safeguard applies to all cases of suspected albuminuria.

2. *Albumoses*.—These generally occur in association with albumen; should they occur alone, the ring will disappear with warming, to reappear on cooling, and there will be no cloud with the heat test.

3. *Bence-Jones's Albumose*.—This occurs without albumen, gives a ring with nitric acid that disappears on warming, to reappear on cooling; with the heat test a dense cloud appears about 60° C., to disappear on further heating to boiling point.

4. *Nucleo-albumen*.—The ring with this is not in contact with the nitric acid, but higher up and diffuse; it may be a real difficulty in diagnosis from albumen, for it is also precipitated by acetic acid, and may therefore give a cloudiness with the boiling test. The methods of avoiding this fallacy are mentioned above.

5. *Urates*.—These may form a cloud near the nitric acid if the urine is very concentrated; the cloud will disappear on gentle warming, to reappear on cooling, so that it may also be mistaken for albumose; this fallacy may be avoided by diluting the urine with plain water before the nitric acid test is employed.

6. *Urea Nitrate*.—If the urine contains a large percentage of urea, a crystalline deposit of urea nitrate may form at the junction. As a rule, the crystalline nature of the ring is obvious on inspection, but in case of doubt the urine should be diluted and the test repeated. It does not matter which test is most relied upon when the result is negative, but before the positive deduction that a urine contains albumen is drawn, both the acetic acid and boiling, and the cold nitric acid tests should be positive.

In arriving at a diagnosis of the precise cause of albuminuria in any given case, it is essential that a microscopical examination of the centrifugalized deposit from the urine should be made. Whatever else may be found, the first question to be answered is—Are renal tube casts present, as well as albumen, or not? All cases of albuminuria may be divided into two main groups, namely—(1) Cases with renal tube casts; (2) cases without renal tube casts.

RENAL TUBE CASTS.

When one speaks of renal tube casts in this respect, however, one has to bear in mind the fact that modern methods of centrifugalizing with electrically driven machinery have reached so high a degree of perfection that hardly anything that a given specimen of urine

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contains escapes detection; technique has become almost too perfect, for when clinical methods become too delicate they begin to lose some of their clinical value. The result, in connexion with casts, is that even in a great many normal urines an occasional renal tube cast and an occasional red blood corpuscle are found; therefore, when one speaks of cases of "albuminuria with tube casts," one means "with enough renal tube casts to be pathological." The observer learns from previous experience to know when the "occasional" tube cast is inside or outside the normal limits. More than one examination may be required, and the urine should be as fresh as possible, for casts disintegrate on standing, especially in hot weather and in alkaline urines.

Renal tube casts are of various sorts, and a certain amount of help can be derived from a knowledge of the particular kinds of casts present in a given case. Their matrix or foundation is a structureless material whose origin is obscure, though thought to be due to some kind of proteid coagulation. Sometimes the casts consist of this structureless matrix only, and according as they are then less or more highly refractile they are spoken of as *hyaline casts* or *waxy casts* respectively. The hyaline form is commoner than the waxy, but neither is characteristic of any particular disease. Embedded in the hyaline matrix there may be various substances or structures, and, according to the main features of the embedded substances, the casts receive different descriptive names. If renal epithelial cells predominate, the cast is called an *epithelial cast*; if leucocytes or pus corpuscles, a *leucocytic cast*; if red blood corpuscles, a *blood cast*; if bacteria, *bacterial casts*; if fat globules, probably derived from degenerated renal cells or leucocytes, *fatty casts*; if non-fatty granular debris, *granular casts*. It is not at all uncommon to find a long cast which in one part is simply hyaline, at one end is granular, and at the other epithelial—a *mixed cast*. Upon the whole, one may say that the hyaline cast occurs in all forms of nephritic conditions, whether acute or chronic; that epithelial and leucocyte casts indicate active catarrh; that granular casts tend to occur along with epithelial casts, but that when they occur alone or in association with hyaline casts, they are evidence of at least less acute mischief than are epithelial casts, while fatty casts come between the two. Blood casts may occur in almost any variety of renal haemorrhage, and by themselves they are not evidence of inflammation, though in association with other casts they indicate very acute inflammatory changes.

A.—ALBUMINURIA WITH RENAL TUBE CASTS.

When it has been decided that there are a pathological number of renal tube casts as well as albumen in the urine, it is almost certain that there is an inflammatory lesion of the kidney. The next step in the diagnosis is to decide by microscopical examination whether pus is present also; in other words, the cases may be subdivided into two main subgroups—namely, (a) albuminuria with renal tube casts without obvious pus, and (b) albuminuria with renal tube casts and obvious pus. There are, of course, a few border-line cases in which leucocytes are present in excess and yet not in sufficient numbers to constitute pus. There will generally be other points about such a case that will lead one to decide whether it comes rather in the pyuric or in the apyuric group. The differential diagnosis of the former will be discussed in another lecture under the heading of pyuria, so that it only remains here to discuss: (a) The differential diagnosis of albuminuria with tube casts without obvious pus. The causes of this condition may be classified as follows:

1. The Various Forms of Bright's Disease:

- (a) A primary acute nephritis.
- (b) An acute exacerbation upon an underlying chronic nephritis.
- (c) Chronic nephritis of young people:
 - (i) Arising out of a known attack of acute nephritis.
 - (ii) Arising without any known previous attack of acute nephritis.
- (d) Chronic nephritis of old people, cirrhosis of the kidneys.
- (e) Arterio-sclerosis.
- (f) Cystic disease of the kidneys.

2. Nephritis of Pregnancy.

3. *Chronic Ascending Nephritis*, leading to scarred contra kidneys, the result of:

(a) Obstruction to outflow by:

- (i) Urethral stenosis.
- (ii) Enlarged prostate.
- (iii) Displacement of the womb.
- (iv) Fibromyoma, ovarian cyst, or other pelvic tumour.
- (v) Pregnancies.
- (vi) Uncue mobility of the kidney and kinking of the ureter.
- (vii) Rarities, such as abdominal aneurysm obstructing a ureter.

(b) Irritation ascending from the pelvis of the kidney, the result especially of calculus, but also sometimes of chronic tuberculous lesions.

4. *Lardaceous Disease of the Kidneys*.

5. *Infarction of the Kidneys*, especially when the result of embolism in cases of fungating endocarditis; but also due to thrombosis, as in some blood diseases.

6. *Thrombosis of the inferior vena cava* involving the renal veins.

7. *New Growths of the Kidney*—some cases.

In many instances the diagnosis soon becomes obvious, but in some there may be great difficulty. The two following cases may serve to indicate how such difficulties may arise:

A patient of middle age, who had not been strong for a long time, began to suffer from oedema of the ankles, which rapidly increased and spread to her back, genital organs, thighs, and legs. She did not see a doctor at once; but within a few days her abdomen began to swell, and she began to pass very little water, and what she did pass was the colour of blood. Upon examination the urine had a specific gravity of 1030 and was loaded with albumen and blood; microscopically there was an abundance of red corpuscles, renal epithelial cells, leucocytes, and epithelial, fatty, granular, and blood casts, without pus, crystals, or bacteria. It seemed almost obvious that she must be suffering from acute Bright's disease; but there was no oedema of the eyelids, and there was definite enlargement of the left supraclavicular lymphatic gland. The discovery of the latter led to a very careful examination for malignant disease, and a latent and quite unsuspected carcinoma of the rectum was discovered. The diagnosis was carcinoma recti, secondary deposits in the retroperitoneal glands, obstruction and thrombosis of the inferior vena cava and of the renal veins, with consequent albuminuria, haematuria, and renal tube casts from asphyxial nephritis simulating acute Bright's disease.

Another case was that of a girl of 16, who began to suffer from increasing anaemia, shortness of breath, oedema of her ankles and face, and slight pyrexia. The heart seemed to be a little enlarged, and there were soft systolic bruits that were regarded as secondary to the anaemia. The urine contained blood and albumen, with renal epithelial cells and tubercasts in abundance. Ascites developed, with increasing general oedema; there were also retinal haemorrhages and neuro-retinitis. The diagnosis of acute nephritis, however, was only in small degree correct; for she was really suffering from malignant endocarditis of a sub-acute type, the nephritis being due to infected emboli of the kidney producing inflammatory changes around multiple renal infarcts.

These two cases will serve to show how it may be impossible to arrive at a correct diagnosis except by a thorough examination of all the systems, by watching the case carefully, and by repeating the full systematic examination at intervals. We will now deal with the main headings in the above table in their reversed order.

If there is new growth in a kidney the number of renal tube casts is likely to be small; sooner or later a microscopic fragment of new growth will probably be detected in the centrifugalized urinary deposit. Albuminuria will not be extreme unless the renal veins and the inferior vena cava become involved, the same applying also to the oedema of the legs and trunk; haematuria is likely to occur at intervals, the attacks being separated by many weeks sometimes, and being relatively painless; there may be an increasing renal tumour; cystoscopic examination may show the blood-stained urine to be coming from one ureter only; and finally, when suspicion of new growth has been aroused, laparotomy may be indicated and the diagnosis thereby confirmed.

Thrombosis of the renal veins and inferior vena cava has been referred to above as a condition that may simulate acute nephritis. Points to lay stress on in arriving at the diagnosis are: (1) To make a very careful and systematic examination, including that of rectum and vagina, in order not to miss anything, such as some latent growth whose secondary deposits are obstructing the veins; (2) to inquire carefully into the history—a great many cases of inferior vena caval thrombosis are due to extension upwards from iliac or saphenous clots, in which case there will nearly always have been swelling of one leg only to

start with, followed later by extension to the back and to the other leg; (3) to note that, although the oedema of the legs and back may be extreme, there is a definite upper level to it and no swelling of the eyelids or scalp; and (4) to note that if there are any distended or varicose veins upon the abdominal wall the blood current in them has become reversed—to being from below upwards instead of from above downwards.

Infarction of the kidneys may be either embolic or thrombotic. By far the commonest cause of embolic renal infarction is infected or fungating endocarditis. Each embolus gives rise to the sudden appearance of blood in the urine, which may have contained none previously, or to a sudden marked increase in any existent haematuria; there may or may not have been a sudden pain in the back at the same time. Around each infarct there develops acute nephritis, so that in some cases all the characters of the latter malady may be superposed upon those of the fungating endocarditis. If the patient is already known to have heart disease, the diagnosis is easy enough; the difficulties arise in cases in which, notwithstanding the fungating endocarditis, there is no bruit. If fungating endocarditis is suspected, the points that confirm the diagnosis are: Pyrexia, which may be of any type—though absence of pyrexia does not exclude the disease; enlargement of the spleen; cutaneous, retinal, or other haemorrhages; progressive anaemia; definite cardiac bruits, especially if the latter at any time undergo any radical change in their character, such as becoming musical instead of blowing, or vice versa; optic neuritis; and multiple embolism, for instance in the brain, spleen, or a peripheral artery. There is no marked leucocytosis as a rule. Venous blood may be cultivated bacteriologically as a means of confirming the diagnosis.

Thrombotic infarcts are less severe in their effects; they may produce no haematuria at all, and the albuminuria may be slight, and unaccompanied by tube casts. They generally arise in cachectic conditions, or in blood diseases such as leukaemia or pernicious anaemia, in which cases the diagnosis will be arrived at on other grounds, and albuminuria will not be the prominent feature of the case.

Lardaceous disease of the kidneys used to be common enough in the days of septic surgery, but it is decidedly uncommon now. It is a risky diagnosis to make, therefore, unless there is some obvious cause for it, such as long-standing suppuration in association with a spinal, hip-joint, or empyema sinus, bronchiectasis, phthisis with cavitation, or the like; or else clear evidence of tertiary syphilis of the viscera with cachexia. There is nothing characteristic about the urine, although statements are made to the contrary. In the earlier stages there may be but a trace of albumen in an otherwise normal urine; later the albumen increases, and it may reach very large amounts, such as 20 parts per 1,000, casts being very few in proportion, the total amount of urine increased, its colour pale, and its specific gravity low—1005 to 1012; later still, possibly as the result of a superposed nephritis, the amount of urine falls until only a few ounces may be passed each day, of high colour and specific gravity 1020 to 1035, loaded with albumen, and now containing hyaline, waxy, granular, fatty, and epithelial casts. Lardaceous casts may or may not occur, but they are not diagnostic, for they have also been found in cases of nephritis without lardaceous disease, hyaline degeneration of the renal tissue being not uncommon in cases of chronic nephritis. Indeed, the diagnosis of lardaceous kidney resolves itself into one of guesswork in a case in which there has been prolonged suppuration or severe syphilis to give rise to it, and in which there may be smooth, firm enlargement of the liver, moderate enlargement of the spleen, and more or less severe diarrhoea, to indicate corresponding lardaceous change in the other organs that are generally affected at the same time as the kidneys.

Chronic ascending nephritis arises from precisely the same causes as acute ascending nephritis or surgical kidney, and probably results from recurrent focal inflammations, which heal, each leaving behind a smaller or larger scar, with the result that in the course of months or years the kidneys are converted into a mass of irregular fibrotic scars, which together produce the same local and general changes and effects as are to be found in cases of ordinary red granular contracted kidney.

This is not always kept clearly in mind. At first sight

it might seem that there could be little connexion between prolapsus uteri and cerebral haemorrhage, but the latter may be due to the former by the following sequence of events: The displacement of the womb and bladder sometimes produces a bend or kink in the ureters a short distance above their vesical ends; this obstruction, persisting for years, tends to produce chronic ascending nephritis. The fibrotic changes in the kidneys that result from this may lead to thickening of arterioles, high blood pressure, and hypertrophied heart, with tendency to apoplexy, just as other forms of granular kidney do. It is true that this sequence of events is not very common; but this is because prolapse of the uterus, fortunately, is not generally left untreated when it is of sufficient degree to cause the ureteral obstruction referred to above. Nevertheless, it is important to bear in mind that any cause of prolonged obstruction to the urine outflow may cause granular kidney with albuminuria, without pus, but with casts, and a pale and abundant urine of low specific gravity.

The diagnosis will generally be obvious when the obstruction is due to urethral stricture; it is more apt to be overlooked in other cases, though if one bears in mind the kind of causes mentioned in the list above the methods of diagnosis will generally be obvious. One would mention in particular that uterine tumours or displacements are a very common cause for slight albuminuria and a few renal tube casts in women; and that in men of 60 and over enlargement of the prostate causes a precisely similar condition long before there is any definite pyuria.

Pregnancy nephritis is sometimes spoken of as though it were an altogether different thing to nephritis of the Bright's disease type in general. I do not subscribe to this view. I hold that Bright's disease has many different causes and many different types. It may be due to scarlet fever, in which case it is very possibly streptococcal; it may be due to pneumonia or empyema, in which cases it may be pneumococcal; it may be due to various other micro-organisms; it occurs in some cases of cholera, and in severe secondary syphilis; it may be due to chemical substances, such as turpentine, cantharides, or oxalic acid; it very often seems to come on from no known cause at all, though in such cases there must be a microbial or other cause that is not discovered; it may be due to pregnancy, in which case it is ascribed to unknown toxins.

In all these cases the types of reaction on the part of the kidney are similar, and one can only regard pregnancy nephritis as a variety of non-suppurative nephritis in general. Very likely it is only a matter of degree whether it is non-suppurative or merges into the type in which there is pyuria as well as albuminuria—pyelitis of pregnancy. Pregnancy may cause a primary acute nephritis which may recover either completely or but partially, and persist as chronic nephritis; or may seem to recover, when in reality it is merely latent, or even slowly and insidiously progressive; it may produce what seems to be a primary acute nephritis which is really but an exacerbation superposed upon a chronic nephritis that has been unsuspected; and very possibly it may produce nephritic changes which are not associated with definite symptoms at the time, but which ultimately result in what is spoken of as chronic interstitial nephritis. When, therefore, albuminuria with renal tube casts, but without pyuria, occurs during pregnancy, it matters little what name is given to the condition, provided it is realized that just the same difficulties offer themselves here as in Bright's disease in general in arriving at a conclusion as to whether the renal lesion is acute, chronic, or acute on chronic.

Various Forms of Bright's Disease.

Of all these, the hardest to diagnose with certainty is *primary acute nephritis* in the adult. The majority of adult cases that are labelled acute Bright's disease are really suffering, not from primary acute nephritis, but from an acute exacerbation upon the top of already existent, but possibly latent, chronic nephritis. The difficulty is to arrive at the diagnosis between these two, particularly since many of the points mentioned in textbooks as occurring in acute nephritis are really due, not to the acute attack, but to the subacute or chronic renal lesion which has until then been unsuspected.

The best examples of primary acute nephritis are to be seen in cases that are already under observation for some other disease, notably scarlet fever or lobar pneumonia.

Sometimes the onset of the nephritis is indicated by general oedema, especially of the eyelids and face, ankles, genital organs, and loins; but it cannot be too strongly insisted upon that oedema is not essential, many cases of acute nephritis having no oedema at all, especially if the patient is already in bed when the kidney inflammation begins, as in scarlatina cases. If the urine were not examined, the renal lesion would often escape recognition altogether; and there can be no doubt that many cases of primary acute nephritis do escape recognition in this way, coming under observation later, when they present symptoms of chronic nephritis, or an acute exacerbation of chronic nephritis.

The essential point in the diagnosis is urine examination. According to the severity of the nephritis there will be more or less diminution in its total daily quantity; it is common for less than 20 oz. to be passed in the twenty-four hours, and often the amount falls to 10 oz., 5 oz., or even to none at all for a while. The specific gravity is raised to 1025, 1030, or even to 1035, but rarely to 1040. The reaction is generally acid at first, but it soon becomes alkaline on standing. The colour is extremely variable, according as little or much blood is present; sometimes it is almost normal or merely that of a concentrated urine; more often there is some tingeing with blood, varying from bright red to brownish, brown, brown-black, or to that peculiar blackish tint which is described as smoky. There is a general cloudiness of the specimen, and on standing it deposits a heavy sediment which often has a dark brownish tint, owing to the phosphates carrying the blood pigment down with them. Microscopically, the centrifugalized deposit consists partly of amorphous debris due to earthy phosphates, and to the disintegration of cells and tube casts; and one expects to find an abundance of red corpuscles, renal epithelial cells, variable numbers of epithelial, fatty, granular, hyaline, and blood casts, an excess of leucocytes, an occasional crystal of calcium oxalate or uric acid, and irregular granular masses which are not definitely tube casts. It is noteworthy, however, that in the very acute stages there may be no tube casts, though shed renal epithelial cells are abundant; in such a case, tube casts will show themselves in a few days.

It is important that each specimen should be examined as fresh as possible, owing to the tendency to alkaline reaction and disintegration of casts and cells on standing. In addition to red corpuscles there is often a considerable amount of free haemoglobin; the tincture of guaiacum test will be positive, and the spectroscope will show the bands of oxyhaemoglobin or of methaemoglobin. Coagulable proteid is generally present in abundance, the proportions of globulin and albumen varying greatly, but together amounting to anything between 2 and 20 parts per 1,000, often about 15 parts per 1,000 at first, rapidly dropping to less after the first few days of treatment, until at the end of from a fortnight to a month it may be 1 part per 1,000 or less, or even absent altogether. In a few cases, however, there is very little coagulable proteid but an abundance of albumose, so that the boiling test gives but a faint cloud, whilst the nitric acid test yields a dense white ring, soluble on warming, reappearing on cooling. There is generally an excess of nucleo-proteid also. The urea, chlorides, and phosphates all fall below the normal totals, though their percentages may be increased if the urine is very concentrated.

With this condition of urine there will be little doubt as to the presence of acute nephritis, the only question being whether it is primary or whether it is an exacerbation upon chronic nephritis. The former is probable, if it is known that the urine was free from albumen up to the time of the attack; if the patient is known to have suffered recently from scarlet fever, pneumonia, diphtheria, secondary syphilis, or some other similar fever; if the heart is of normal size and its sounds natural, the blood pressure natural, and the retinae healthy. It may be that the patient himself may have been exposed to scarlatinal infection, and without having had the rash, may develop nephritis; the association of peeling of the skin, or recent sore throat with enlarged glands in the neck, or otitis media, might suggest the diagnosis in these mild cases of scarlatina, though sometimes acute nephritis in a child may be the sole evidence of the disease. The course of the malady will also assist the diagnosis; the albuminuria of primary acute nephritis may clear up

entirely in from a fortnight to six weeks, though in unfavourable cases it persists, and chronic nephritis develops out of the acute. If, on the other hand, it is found that, in a case of apparently recent acute nephritis, with general oedema, haematuria, and the other urinary changes described above, there is cardiac hypertrophy with a prolonged lumpy first sound at the impulse, a ringing aortic second sound, a blood pressure of more than 160 mm. Hg, and possibly albuminuric retinitis, the probability is that the acute nephritis is not primary but an acute exacerbation of an unsuspected chronic nephritis. There is often a history of former scarlet fever or of syphilis in such cases; the patients may be of any age, from childhood to past middle life. If the patient survives, one or other of two conditions usually results: either the albuminuria, the scanty urine, and the tube casts persist, whilst the patient remains waterlogged until the end comes in a few weeks or months, or else the acute exacerbation subsides, and the clinical characters of chronic nephritis remain. Some of these, but by no means all of them, are examples of primary acute nephritis, persisting and becoming chronic.

It must, however, always be very difficult, and indeed almost a matter of opinion in many cases, to decide whether a patient is suffering from a chronic nephritis which is the result of a primary acute nephritis that has not cleared up, or from a chronic nephritis which was present but unrecognized before an acute exacerbation drew attention to it; but my own view is that many cases in which young adults seem to develop acute nephritis from no more definite cause than exposure to damp or cold, are really examples of acute on chronic, and not of primary acute Bright's disease. The albuminuria in these cases does not clear up, and it is a mistake to restrict the diet or the daily occupation after the acute exacerbation has subsided. In spite of the persistence of albuminuria, these patients do best if they are given iron and allowed to go about their ordinary avocations; they have diseased kidneys, and they will not live many years, but there is no need to adopt treatment which constantly reminds them of the fact. As the acute exacerbation subsides in these cases, the amount of urine rises rapidly to 60 or 70 oz. or more per diem, and remains increased even after all oedema has passed away; the specific gravity falls to 1012, 1010, or 1008; the albumen persists to the extent of anything between 0.5 and 8 parts per thousand; blood is absent, though an occasional red corpuscle may be seen under the microscope, and there are moderate numbers of hyaline, granular, or even fatty casts, with an occasional renal epithelial cell.

It happens not infrequently that a young patient suffering from chronic nephritis comes under observation for shortness of breath, palpitations, anaemia, or for inflammation of one or other of the serous membranes, without ever having had any symptoms of acute nephritis at all. The kidneys that would be found in such cases differ from the granular contracted kidneys of older people in that they are pale instead of red. They are *pale, granular, contracted kidneys*, precisely similar to those which may result from a long antecedent acute nephritis that has not entirely cleared up. When they develop without any known preceding attack of acute nephritis, they have been referred to as Rose Bradford kidneys. It is by no means impossible that they are really the result of a preceding acute nephritis which escaped recognition because there was no oedema to attract attention to the need for urine examination. The patient may be of any age, though generally between five and thirty-five. There may be no sign of anything wrong until acute uraemia, with convulsions, leads to rapid death. On the other hand, in a typical case, in addition to the urine changes mentioned above, one expects to find some of the following symptoms or signs: a great increase in the size of the left ventricle, as evidenced by displacement of the impulse downwards and outwards into the sixth left intercostal space below or outside the left nipple, with increase of the precordial impairment of resonance outwards to the left without corresponding increase upwards or to the right; a ringing exaggerated second sound in the second right intercostal space close to the sternum, and a prolongation of the first sound at the impulse, or its replacement by a more or less localized blowing systolic bruit; more or less anaemia, sometimes very considerable and of the chlorotic type; a

maximum systolic blood pressure of 175 mm. Hg or more, sometimes to over 300 mm. Hg, even when the pulse feels comparatively soft to the finger; albuminuric retinitis; a tendency to haemorrhages, especially to epistaxis; headache; insomnia; breathlessness on exertion; and inability to work with the usual energy, either mentally or physically.

The chronic nephritis of old people is diagnosed more often than it exists, if one understands by it the disease associated with small red granular contracted kidneys. On the other hand, the kidneys of most old people exhibit a certain amount of interstitial fibrosis, with occasional retention cysts and some granularity of the surface when the capsules are stripped off, without there being any material diminution in their size. Where senile changes that are almost normal end and chronic interstitial nephritis begins, is difficult to determine. The same applies to arterio-sclerosis and the renal changes associated with this arterial degeneration. Some regard arterio-sclerosis and chronic interstitial nephritis as essentially different maladies; others regard the arterial as secondary to the renal changes; others hold that arterio-sclerosis leads to a variety of red granular kidney that is not the same as the red granular contracted kidney of chronic interstitial nephritis; whilst others, again, favour what seems a likely view—namely, that arterio-sclerosis and sclerosis of the kidneys both have a common cause, and that it is more or less of an accident whether the patient, on *post-mortem* examination, presents more arterial than renal changes, or about the same degree of both. During life the differential diagnosis between them is sometimes impossible. In either case there will be a hypertrophied left ventricle, a loud lumpy first sound, or a blowing systolic bruit at the impulse, a markedly accentuated aortic second sound, a systolic blood pressure somewhere between 150 and 320 mm. Hg, with a tendency to shortness of breath; giddiness, especially on sudden change of posture; ringing in the ears; difficulty in concentration of mind; and very possibly cardiac symptoms, varying from a mere consciousness of the existence of the heart, to precordial pain of varying severity, or even extreme heart failure, with oedema of the legs, ascites, nutmeg liver, orthopnoea, and pulmonary congestion. In the latter case the great difficulty will be to decide whether the heart failure is due to primary renal or arterial, primary cardiac, or to primary pulmonary disease, and the only sure methods of deciding that there is a renal lesion are, first, the discovery of more than an occasional granular and hyaline tube cast in the urine; and secondly, the detection of albuminuric retinal changes. Sometimes inflammation of one of the serous membranes is the first symptom; subacute or chronic peritonitis with ascites; pericarditis; or pleuritic effusion. On the other hand, the patient may seem to have been in robust health until the nature of the case is suggested by a sudden apoplectic seizure due to cerebral haemorrhage, followed by hemiparesis or aphasia.

In yet another group of cases the malady is discovered accidentally as the result of examination for life insurance. It is not very uncommon to find glycosuria as well as albuminuria, the sugar occurring in a urine of normal specific gravity, without any associated acetone or diacetic acid. The degree of albuminuria is very variable indeed; when there are signs of cardiac failure there may be oliguria, with much albumen, and not a very large number of casts; when there is no heart failure there is generally polyuria, the patient having to rise several times in the night, passing from 60 to 120 oz. of urine in twenty-four hours. It is pale, of specific gravity 1008 to 1012, often containing only a trace of albumen, and even that not constantly; there are intermediate cases in which the amount of albumen varies from 0.25 to 4 or 5 parts per 1,000. Upon the whole, one may say that if the increased albuminuria due to heart failure, on the one hand, or to a superadded acute attack of nephritis on the other, can be excluded, the more the disease approaches the type of red granular contracted kidney the more likely is the albumen to be small in amount and intermittent; whilst the more the disease approaches in type to arterio-sclerosis with renal changes on the one hand, or to pale granular contracted kidneys on the other, the greater will be the amount of albumen if any is present. There will be tube casts, chiefly granular and hyaline, most numerous with pale granular contracted kidneys,

fewest with arterio-sclerosis, and intermediate in number with red granular contracted kidneys. It need scarcely be added that the absence of albuminuria does not exclude arterio-sclerosis; but we are here dealing only with cases in which albuminuria occurs.

Cystic disease of the kidneys is found in three entirely different types of patients—namely, (1) the newly born, (2) the young, and (3) the elderly. In the newly born the main symptom is abdominal distension, which may be so extreme as to have caused difficulty in delivery; the bilateral cystic tumours can be felt, and the diagnosis in extreme cases is by no means difficult. Minor cases escape detection at birth, and it may be that several years have elapsed before the diagnosis is arrived at, as the result of finding bilateral uneven renal tumours associated with the passage of abundant pale urine of low specific gravity containing traces of albumen, a few granular and hyaline tube casts, and an occasional red corpuscle. Sometimes a sudden and severe attack of haematuria is the first symptom in the case. The discovery of bilateral irregular renal tumours is the clinching point in the diagnosis. In at least one case they were so large as to meet in the middle line, so that a loop of intestine, having passed in between and behind them, could not get out again, and the patient came under observation for acute intestinal obstruction. The third type of cystic disease of the kidneys, which occurs in old persons, is but a variety of chronic interstitial nephritis in which the agglomeration of retention cysts has reached an extreme degree; the enlargement of the kidneys in these cases is very much less than in young persons, where the lesion is probably congenital, and the symptoms and urinary changes are precisely similar to those that may occur in cases of red granular contracted kidneys already described.

B.—ALBUMINURIA WITH RENAL TUBE CASTS AND WITH PUS.

When pus is present in the urine, along with albumen and renal tube casts, the differential diagnosis resolves itself into that of pyuria that is partly or wholly of renal origin. It only remains to add: First, that it is by no means sufficient to rely upon the naked-eye characteristics of the urine or upon chemical tests in excluding minor degrees of pyuria; microscopical examination of the centrifugalized deposit is essential, especially in the detection of acute pyelitis and pyelonephritis, the result of *coli bacilluria* in children, pregnant women, and others. Secondly, that the amount of albumen actually due to pus itself is small, so that if there is any measurable quantity of albumen present it indicates that the kidneys are themselves affected, this being further confirmed when casts are also found. And, thirdly, that blood, like pus, is in itself responsible for relatively little albumen, so that when there is considerable albuminuria associated with blood there is strong ground for believing that the albumen is by no means all due to the blood. The presence or absence of very small quantities of blood does not assist the differential diagnosis of the cause of albuminuria so much as might be expected; the occurrence of much blood with much albumen and many renal cells and tube casts indicates *acute nephritis*, but by itself does not decide between primary acute nephritis, acute exacerbation of a chronic nephritis, or the effects of embolic infarction in cases of malignant endocarditis. *Renal growths, calculus, or tuberculosis* may all cause haematuria and pyuria with albuminuria, and a variable number of granular, hyaline, fatty, epithelial, leucocyte, or blood casts; and occasionally, when the amount of pus is small, it may be difficult to distinguish between these and acute nephritis. Their differential diagnosis was discussed in a previous lecture on haematuria.

C.—ALBUMINURIA WITHOUT TUBE CASTS.

Turning now to the question of the occurrence of albuminuria without renal tube casts, one would first emphasize the fact that more than one microscopical examination may sometimes be required, for if the urine is alkaline, or has stood for any length of time, casts originally present may have become unrecognizable; besides which, even with definite nephritis, there may be very few casts at one time, many at another. This applies particularly to the very acute cases on the one hand and the very chronic on

the other. Assuming however, that no cast, or not more than a very occasional cast, is found, the chief conclusion that can generally be drawn is that the albuminuria is not indicative of organic renal disease.

The cases may, then, be subdivided into: (1) *Those in which the urine presents some other definite abnormality besides albuminuria, especially (a) pyuria, (b) haematuria, (c) haemoglobinuria, or (d) glycosuria*; (2) *those in which, were the albumen removed, the urine would be normal.*

1. These cases need not be discussed further here; the differential diagnosis comes under the heading of pyuria, haematuria, haemoglobinuria, and glycosuria respectively.

2. These are clinically of importance in that, until the absence of casts has been determined, the absence of organic renal changes cannot be concluded. Even when casts are absent, a trace or a small amount of albumen may be the first evidence in elderly persons of enlargement of the prostate, chronic interstitial nephritis or arteriosclerosis; or in younger persons of chronic ascending nephritis, the result of such things as former gonorrhoea, repeated pregnancies, uterine prolapse or other displacement, chronic vesical catarrh, or urethral stricture. The chronic effects on the kidneys of interference with the urine outflow are apt to be overlooked; if they are borne in mind they are generally easy of diagnosis.

The following are a number of other conditions which may cause slight degrees of albuminuria without tube casts, but which are obvious, or else diagnosed by other obvious symptoms or signs: Burns, scalds, chronic alcoholism, cirrhosis of the liver, diabetes mellitus, exophthalmic goitre, gout, lead poisoning, mumps, secondary syphilis, morphinism, mercurialism, vasomotor neuroses such as Raynaud's disease or angioneurotic oedema, obstruction to the vena cava inferior by thrombosis or by external tumours, the pressure of considerable ascites, ovarian cysts or solid tumours, pernicious anaemia, Hodgkin's disease or lymphadenoma, lymphosarcoma, lymphatic or splenomedullary leukaemia, splenic anaemia, pemphigus, phosphorus poisoning, chronic arsenical poisoning, pregnancy, severe anaemia the result of syphilitic, malarial, malignant, tuberculous, or phthisical cachexia, ankylostomiasis, or infection with other parasites, such as *Bothriocephalus latius*, or *Trichina spiralis*.

There remain three other groups of conditions in which albuminuria and its differential diagnosis are often important, and these are: (1) *Febrile conditions*; (2) *heart-failure conditions*; and (3) so-called "*physiological*" albuminuria of young males.

1. Febrile Conditions.

In nearly every fever there is some cloudy swelling of the parenchyma of various viscera, especially the kidneys; consequently most fevers may sometimes be associated with albuminuria, and, broadly speaking, the higher the patient's temperature the greater is the liability to it. The amount of albumen present is generally not great. We need not enumerate all the various fevers in this connexion, nor discuss the causes of hyperpyrexia. Suffice it to say that albuminuria is relatively common in scarlatina, diphtheria, variola, erysipelas, pyrexial phthisis, cholera, dysentery, Weil's disease, severe malaria, and yellow fever; not so common in lobar pneumonia, bronchopneumonia, typhoid fever, and empyema; and relatively uncommon in other febrile conditions, such as acute rheumatism, influenza, meningitis, measles, German measles, follicular tonsillitis, and so on. The albuminuria may of course be already present in a person who develops an intercurrent fever; the diagnosis then depends upon considerations mentioned above.

If, on the other hand, the albuminuria is known to have developed coincidentally with the febrile illness, the chief point to decide will be whether it indicates actual nephritis or not. Many consider there is an essential difference between "febrile albuminuria" and actual nephritis. This may or may not be so, but it is extremely difficult to be sure of the distinction clinically. It may be urged that—to take scarlet fever as an example—the albuminuria of the first few days is "febrile," whilst that of the second or third week is "nephritic." As a matter of fact, in not a few cases in which death has occurred in the first week the "febrile" albuminuria has been associated with large mottled acute nephritic kidneys, even when there has been no oedema, no haematuria, and no very

large numbers of renal tube casts. Probably there are all degrees of acute nephritis, from very slight and transient to very severe and possibly fatal; and it is a mistake to try and make a distinction in kind. The great majority of cases of albuminuria during fever recover completely; some seem to recover, but come under observation years later with pale granular contracted kidneys; others die during the acute attack. The degree of albuminuria is not a direct measure of the renal changes unless the amount of albumen is large; a small amount of albumen does not necessarily indicate trivial nephritis. Absence of oedema is the rule. Microscopical examination of the centrifugalized urinary deposit is essential; the more the renal epithelial cells, red corpuscles, leucocytes, and various renal tube casts, the more conclusively can some degree of actual nephritis be diagnosed.

When doubt lies between scarlatina and measles or German measles, or between diphtheria and other forms of sore throat, the existence of albuminuria sometimes assists in arriving at the diagnosis of scarlatina in the one case, or of diphtheria in the other.

In pneumonia, albuminuria has become much less frequent since blistering with cantharides has gone out of fashion in treating this disease.

2. Heart-failure Conditions.

The right side of the heart may fail owing to many different causes, which may be arranged under four main headings as follows: (a) Valvular disease; (b) obstructive lung affections; (c) myocardial affections; (d) granular kidneys and other high blood pressure conditions. Each of these main headings has many subheadings which need not be repeated in detail. Any one of them may result in albuminuria, though the amount of the latter is extremely variable, some cases of severe heart failure exhibiting no albuminuria at all, whilst others may have as much as 10 parts per 1,000 or more.

The first step in the differential diagnosis is to exclude primary renal conditions by negative microscopical examination of the centrifugalized urine deposit for casts, examination of the retinae, and exact determination of the blood pressure. Curiously, even with feeble, irregular pulses, such as are found in panting cases of mitral stenosis, the blood pressure is considerably higher than normal, doubtless owing to partial asphyxia; so that merely finding a systolic blood pressure of 150 or 160 mm. Hg is no proof of granular kidney or arteriosclerosis; sometimes, however, the reading is as high as 200, 250, 300, or even 320 mm. Hg, and then the diagnosis of one or other of the latter is almost certain.

If renal and arterio-sclerotic conditions can be excluded, the diagnosis lies between the other three main groups. The cardiac bruits, the history of growing pains, chorea, and acute rheumatism, the youth of the patient, the family history of heart disease or rheumatic fever, the association of other rheumatic affections, such as recurrent tonsillitis, subcutaneous nodules or erythema, will often serve to point to primary valvular disease and its nature; in older patients, especially in men between 40 and 50, there may be aortic disease and a history of syphilis, and not of acute rheumatism. In severe heart failure in children under puberty the result of mechanical difficulty with the circulation, an adherent pericardium is generally found, and clinically the heart is large out of proportion to the general physical signs.

When there is a definite history of recurrent winter cough in an elderly person, with a hyper-resonant and overexpanded chest, the likelihood of emphysema and bronchitis will at once suggest itself. Similarly fibroid lung, or fibroid lung and bronchiectasis, as a cause of heart failure and albuminuria only needs mentioning, the diagnosis generally being obvious from the physical signs, the clubbed fingers, and, in the bronchiectatic cases, the abundant, intermittent, and frequently foul, expectoration.

Myocardial affections, such as fibroid, fatty, or primary alcoholic heart, are generally diagnosed by guessing at them when other causes of heart failure can be excluded. The patients are generally middle-aged, with precordial pain and even angina pectoris occupying a prominent position amongst their cardiac symptoms; there may or may not be a high blood pressure, the albuminuria is not associated with renal tube casts, there is often no cardiac bruit, or at most a more or less localized blowing systolic

bruit at the impulse; at the same time the heart is clearly enlarged, and it may be beating rapidly and irregularly; there may be a history of syphilis or of chronic alcoholism; the patient may be very stout in the fatty, though generally not so in the fibroid, cases. There may be a history either of an extremely sedentary life upon the one hand, or of overuse of the heart by strenuous hard physical work—as a blacksmith, an athlete, and so forth—on the other. Needless to say, the exact nature of the cardiac lesion remains obscure or uncertain in many of these cases, many a patient who really has mitral stenosis being regarded during life as suffering from chronic bronchitis and emphysema, and so on.

3. "Physiological" Albuminuria.

Finally, we come to that large group of cases of albuminuria in apparently healthy males between the ages of 15 and 30. The condition was unknown until medical examinations at schools or for life insurance, for the army, navy, and civil services became common; and it has received a large number of different names, of which the following are some: "Accidental," "essential," "postural," "cyclic," "orthostatic," "intermittent," "physiological," "functional," "orthotic" albuminuria, Pavy's disease, albuminuria "of adolescence" or "of puberty." It derives its chief importance from the fact that young males who suffer from it are looked at askance by the older examiners for life insurance or for the "services," and are very liable to be rejected altogether. The reason for this was the fear that they were sufferers from some form of nephritis.

Collier and others have thrown much light upon the nature of the affection by their investigations upon the urines of rowing men. It is found that the urine voided just before a boat race being free from albumen, that voided immediately afterwards is generally loaded with it. A few hours later this albuminuria is gone again. Now, university oarsmen are, upon the whole, long-lived; hence this recurrent albuminuria cannot matter in them, and the same applies to the albuminuria of many adolescents. A prominent feature of such a case is that the urine first voided in the morning is quite normal, whilst that passed later in the day may contain anything from a trace to five parts per thousand of albumen, or more; the more the youth has exerted himself physically by walking or otherwise, and the more he has exposed himself to cold, for instance, during a train journey to the city on a winter's day, or in a cold bath, and so on, the greater is the liability to this unimportant, but possibly alarming, albuminuria. Some youths are so liable to it that they may pass albumen for days together before an interval of freedom from it occurs. Sometimes they appear to be in robust health, sometimes they look a little pale, as though they had been overworking at an indoor occupation; they may be nervous, but often they are not. A natural nocturnal emission is supposed to predispose to albuminuria next day. The point is that these individuals have to be differentiated from sufferers from Bright's disease. The method of diagnosis is as follows: A complete routine examination is carried out, and no obvious affection of the heart or other viscera can be detected; the blood pressure is normal; the albumen having been discovered, the patient is directed to supply a series of samples at intervals of a few days, and preferably passed immediately after rising in the morning. If all samples contain albumen it will be very difficult to exclude organic disease; if some contain albumen in abundance, however, and others none at all, the presumption will be that it is "functional"; before being finally satisfied, however, it is important that a careful microscopical examination of the centrifugized deposit from a specimen containing albumen should be made, no casts or other abnormal constituents being found. The administration of calcium chloride greatly diminishes the tendency to this form of albuminuria. In an adolescent male who has no symptoms of albuminuria discovered accidentally, present after exertion or after exposure to cold but absent after rest in bed, and, when present, not associated with renal tube casts or with signs of arterial, cardiac, or other diseases that should be detected by physical examination, is almost certainly a "physiological" albuminuria, which needs no treatment and is not indicative of any underlying disease.

Clinical Observations

ON THE

USE OF DIGITALIS IN HEART DISEASE AND DROPSY WITH FIBRILLATION OF THE AURICLES (NODAL RHYTHM).

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IN the present paper I purpose to illustrate the use of digitalis in cases of heart disease with dropsy, in which the auricles are in a state of "fibrillation" and functionally inactive—a condition present in a large proportion of cases of severe heart failure, whatever the nature of the underlying lesion may be. Cases of this kind constitute a definite group, and their diagnosis is of great clinical importance both for treatment and prognosis.

It has always been recognized that benefit from the administration of digitalis in cases of severe heart failure is variable, even when classical indications for its use are present. In some patients improvement is rapid and maintained—the heart decreases in size, and dropsy quickly disappears; in others its power for good is limited—improvement occurs to a certain extent, and then comes to a standstill; in others again, particularly cases of mitral stenosis with regular pulse, and those resulting from arterial disease, digitalis is often impotent or even harmful—the heart continues to dilate, and dropsy increases under its use.

An example of such a case is the following:

CASE I.

A girl, aged 13, under my observation for some time with a compensated double mitral lesion of rheumatic origin. In August, 1909, severe dyspnoea with marked cyanosis came on after exertion and persisted for several days. The attack was quite recovered from, but later compensation gradually failed, and at the end of October severe dropsy set in. The pulse was quick but regular; heart enlarged to right and left; mitral presystolic, systolic, and diastolic murmurs were present. Although digitalis was well tolerated and given for over a month in full doses, with occasional remissions of a day or two, it had very little influence on the rate of pulse (Fig. 1). For a time

Fig. 1. - Tracing of radial and jugular pulses from Case I after continued full doses of digitalis; rhythm is regular, rate 84 per minute. The jugular tracing shows two pulses, *a* and *v*, to each beat of the carotid artery *c*. The wave *a*, due to contraction of the auricle, precedes the carotid beat by one-fifth of a second (normal, or auricular type of venous pulse).

there was some improvement in the general condition; but subsequently the heart further enlarged, dropsy manifestly increased, the amount of urine diminished, and eventually the lungs became oedematous before death, which occurred two months after the onset of dropsy.

The fact that digitalis often fails to do good in the later stages of heart failure, when the pulse is rapid and regular, was known in the early days of its use. It was recognized that the drug slowed the pulse in some cases more than others, and that to a great extent improvement was proportionate to the degree of slowing which ensued; and, further, that the most marked slowing and rapid response to treatment usually occurred when the pulse was irregular, but it was also recognized that these results were not constant in all cases with irregular pulse.

There was no explanation of this discrepancy forthcoming until Mackenzie differentiated the various forms and causes of irregularity of the heart by means of the venous pulse. He established the fact that in cases which