REFLECTIONS ON NEPHRITIS.

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THESIS PRESENTED

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INTRODUCTION.

The subject of "nephritis" or Bright's disease has long been a field of controversy for clinicians and pathologists alike. The varied clinical pictures and pathological appearances led, in the past, to much confusion and multiplicity of names.

In 1872 Richard Bright first recognised the association of general dropsy, "hard" pulse and albuminuria with a morbid condition of the kidneys. Further he even appreciated the aetiological role played by "scarlatina or some other acute disease", and also that a case beginning acutely could progress slowly through the stage of "wet nephritis" to "dry nephritis".

Although Bright apparently recognised this progressive aspect of nephritis many did not. Rather were the various stages regarded as separate diseases having little or no connection with one another. Nor did the pathological picture help at first. At a glance these would indeed suggest separate conditions - the congested haemorrhagic kidney, the large white kidney, and the small granular contracted kidney seemed to have little in common.

It was only with careful and repeated microscopic examination/

examination of specimens, micro-dissection and wax reconstruction, that pathologists began to throw a glimmer of light on the subject. With the aid of the case histories they began to see a central theme running through the varied and complex pictures that met their eyes. More and more evidence was collected to show that acute nephritis, subacute parenchymatous, and chronic interstitial nephritis were different stages of the one pathological process, and that intermediate stages of the above accounted for many of the "rarer forms of nephritis" encountered in the more elaborate classifications of nephritis.

Much confusion existed still, however, chiefly due to the many and varied names given to the one stage of the disease. Particularly was this so in the case of "subacute glomerulo-tubal nephritis", "chronic parenchymatous nephritis", "chronic nephritis" etc. Different observers would be referring to different conditions under the same or similar names and vice versa.

With the intention of clarifying this maze and emphasising the continuity of the same pathological process running throughout the various types of Bright's disease Volhard and Fahr introduced the terms "first stage", "second stage" and "third stage nephritis". These terms were based chiefly on microscopic findings and interpretation thereof.

At the present time this is the generally accepted view/

view of the subject of Bright's disease, although the above terminology is not so widely used. Boyd in his "Pathology of Internal Diseases" (3rd edition) uses this terminology and seems to portray the present day attitude of the pathologist to this difficult subject.

Before reviewing the pathological evidence for the progressive nature of Bright's disease, it would be well to give some definitions of the terms used to describe the various stages.

Definitions of Terms Used. Using the terminology of Volhard and Fahr, first, second, and third stage nephritis are equivalent terms for acute glomerulo-nephritis, subacute glomerulo-tubal nephritis (chronic parenchymatous) and chronic glomerulo-nephritis (chronic interstitial) respectively.

In First stage nephritis we recognise the clinical picture of (usually) sudden onset of oliguria, smoky or frankly blood-stained urine, with albumin, casts, and a varying degree of hypertension, and moderate oedema.

Second stage nephritis is characterised clinically by marked oedema and abundant albuminuria, casts, normal blood pressure and renal function tests and a tendency to inflammations of serous membranes. This is the stage of "Compensated renal hypofunction" (Fishberg); the large pale kidney of older writers.

Third/

Third stage nephritis represents the clinical picture of progressive renal failure - high blood pressure, enlarged heart, albuminuria (slight) from time to time and a few casts. A tendency to chronic bronchitis is present. Renal function tests are impaired; there may be retinitis. The general health deteriorates.

The second stage is often referred to as the "nephrotic syndrome", and the third, "azotaemic nephritis".

Enough has been said to shew clearly the "types" of nephritis to which the terms refer. We can now, therefore, briefly review the pathological evidence for the different stages being part of one progressive disease.

THE PATHOLOGICAL ASPECT.

It is well known that First Stage or acute glomerulo-nephritis is, in the majority of cases, preceded by an acute streptococcal infection. This is most commonly an attack of acute tonsillitis, although it is observed during the early convalescence of scarlet fever. Organisms have not been found in the kidneys and the evidence suggests that a circulating exotoxin is the cause of the condition.

In the First stage the essential lesions are in the glomeruli "which are destined to influence the course/

course of the disease from its inception to its fatal termination" (Boyd - Pathology of Internal Diseases.) The first thing observed is that the process is a diffuse one. The majority of the glomeruli appear to be attacked. The epithelium covering the vascular tuft undergoes marked proliferation filling up the spaces between the capillary loops. It may be cast off into the capsular space. On the other side of the basement membrane, the vascular endothelium lining the capillaries undergoes proliferation also. The cells may become two or three layers deep and offer serious obstruction to the flow of blood through the tuft. Another intracapillary phenomenon is the formation of hyaline fibres of uncertain origin. According to McGregor these fibres are pathognomonic of first stage nephritis and are responsible for the ultimate hyalinisation of the glomerulus. Mallory's aniline blue stain is necessary to shew these fibres which are thought to be produced by the proliferating vascular endothelial cells.

As the disease progresses these fibres are said to become coarser and more numerous forming a dense network. Eventually the proliferated epithelial and endothelial cells undergo degeneration and are replaced or infiltrated by these hyaline fibres.

Another change is exudation into the capsular space of the glomerulus, of leucocytes and red blood cells/

cells. This would appear to be of minor importance.

The essential lesion in the glomerulus then is a progressive obstruction caused by swelling and proliferation of the endothelial cells and intracapillary formation of hyaline fibres. The result is to render many glomeruli quite avascular and seriously to reduce the blood flow through many others.

The tubules may show slight degeneration said to depend upon the degree of vascular occlusion of the glomerulus. The blood supply to the tubules, it is pointed out, comes from the glomerulus. The efferent vessel from the glomerulus forms a second plexus of loops around the tubule. This point will be referred to again later.

The interstitial tissue shews no change in this stage.

The changes in the Second Stage appear to be chiefly degeneration, and also some proliferative changes similar to that seen in the first stage.

Microscopic examination of a section of kidney at this stage shows marked changes from the normal. The glomeruli show a further advancement of the process seen in the first stage. The glomeruli are enlarged and said to contain no blood, for the intra-capillary process already described has advanced much further. All the glomeruli are not at the same stage. Some are at an early phase of the process.

The/

The most striking feature, however, is the proliferation of the parietal layer of epithelium of the capsule to form the well known "epithelial crescent". This process leads to obliteration of the capsular space.

The tubules shew the marked degenerative changes characteristic of this stage. This change is supposed to be due to the fact that the blood supply to the convoluted tubules has first to pass through the glomerulus, and as the blood supply is cut off the tubule gradually degenerates and atrophies.

The epithelial cells of the tubules shew cloudy swelling, fatty degeneration and actual necrosis. The cells contain large amounts of neutral fat and lipoid material - cholesterol ester.

The interstitial tissue shews some degree of small round cell infiltration especially in the cortex around the more degenerated glomeruli.

In the Third Stage the picture is one of replacement of normal renal architecture by fibrous tissue. The fibrous tissue is partly new, replacing the degenerated nephrons, but much of it is preexisting stroma which becomes more apparent as the parenchyma disappears.

The glomeruli shew hyalinisation - often complete and beginning to be replaced by fibrous tissue. This hyalinisation is the end result of the early intra-

capillary/

intracapillary hyalin formation noted in the first stage. It is to be noted, however, that many glomeruli are normal or hypertrophied. Others shew signs of "epithelial crescents" of the second stage. In this stage it appears that the process has not been so diffuse as first and second stage appearances would suggest. It is reasonable to suppose that this is because a case going on as far as the third stage has not had such a severe attack as the autopsy material from fatal first and second stage cases.

The convoluted tubules shew extreme atrophy. Many have disappeared and have been replaced by fibrous tissue. Others shew hypertrophy - both increase in length and diameter. The work of Oliver has shewn that quite a few of these hypertrophied tubules are aglomerular. Their corresponding glomerulus has undergone hyalinisation and fibrosis. This would appear surprising after the former contention that tubular degeneration was mainly due to the cutting off of the blood supply at the glomerulus.

The increase in fibrous tissue has already been mentioned. This tissue shews collections of small round cells chiefly around degenerating nephrons. The blood vessels shew the diffuse hyperplastic sclerosis. Simple disuse atrophy - endarteritis obliterans - is also present, in vessels running to areas of marked degeneration.

The/

The interpretation put on these findings is that a great many nephrons are completely degenerated and out of action, while many of the remaining, spared, nephrons shew compensatory hypertrophy.

Thus the continuity and progressiveness of the condition is worked out. In the acute stage the glomerular membrane is damaged and glomerulus rendered relatively avascular, and from these initial lesions it is claimed that the degenerative changes of second and third stage nephritis follow.

To summarise this aspect we may say that there is apparently a progressive degenerative change in the nephrons from first to third stage. This, one would conjecture, would mean a progressive failure of function of the renal elements. As each stage is reached kidney function should be more and more impaired.

It should be emphasised that there is no sharp line of demarcation between the stages - the one progresses into the other.

With this brief résumé of the pathological aspect and its interpretations let us now turn our attention to the clinical aspect of the problem.

THE CLINICAL ASPECT.

After considering the pathological view of the problem, one naturally asks whether the clinical aspect is in agreement with the pathological interpretations and to what extent.

Clinically, do we see cases of acute glomerulo-nephritis (first stage) progress through the second to the third stage? The answer is that such cases have been followed right through these stages, but they are not common. The disease is a long one; it may be some 20 to 30 years after the acute stage, that the terminal third stage appears. Such cases are obviously difficult to follow.

Do we, then, in a subacute second stage or chronic third stage nephritis get a history of previous renal disease? Sometimes we do, but often we do not. This is explained, by ardent supporters of the progressive nature of the disease, by assuming that the "first stage" and/or the "second stage" were subclinical; they were so mild as to escape recognition. Dunlop, writing of acute Bright's disease, says: "It is probable that only the severe types of the disease are commonly recognised. In the mild types a small shower of red blood cells occurs in the urine and there are no striking concomitant clinical features, so that the condition may escape medical attention altogether". Boyd, writing on the same subject/

subject, states that "There can be no doubt, that just as acute gastric ulcer is a common condition which seldom attracts the notice of the patient, so acute nephritis in its milder forms may readily pass unrecognised..... Although absolute proof cannot be furnished, and in the very nature of the problem it is hardly possible that it should be, we feel from general pathological considerations that it is most probable that every case of chronic glomerulo-nephritis is preceded by the first or acute stage."

It might be asked that granting the existence of sub-clinical first or second stage nephritis, is it likely that such a mild attack would lead eventually to a "clinical" second or third stage condition? But one must remember that, among the frank obvious cases of acute nephritis, it is not always, by any means, the severest cases that progress and the mildest that recover. Often it is the exact opposite.

The majority of recognised cases of acute glomerulo-nephritis recover and as far as is known never shew any further renal trouble. A few recover but have a persistent slight albuminuria and in the course of a few months or years develop the clinical picture of second stage nephritis. More often is it observed that an acute case does not clear up but goes drifting on. The albuminuria becomes greater and the oedema more marked and extensive, and one recognises/

recognises the fact that the case is now one of second stage nephritis. The change from second to third stage is occasionally observed also.

Definitely, then, some cases do progress from one stage to the other. Others apparently do not, but arise as second stage de novo, unless one postulates a previous "subclinical" acute attack. The majority of cases seen end in the cure of the first stage.

Cases of "third stage" nephritis appear to arise de novo also. That is to say there is no previous history of nephritis obtainable. Again there is the possibility of "subclinical" attacks of both acute and subacute nephritis, and also the possibility of an acute first stage condition passing straight to the third stage without traversing the "second stage." Dunlop states that this can happen and also that a "second stage" condition can arise without a previous "first stage", and subsequently progress to the third stage. He says: ".... We do not suggest that all cases showing this nephrotic syndrome ("second stage") must necessarily have suffered from a previous attack of acute Bright's disease. It is possible that some cases develop an insidious degenerative lesion without any acute renal inflammation." (The words in parenthesis are the writer's). Although in general he is apt to subscribe to the three progressive stages, invoking/

invoking subclinical stages if necessary, he apparently believes that first stage cases can go straight to the third and that the whole course of the disease in other cases is represented by a "second stage" progressing to the third.

Another difficulty regarding cases of apparent "third stage" nephritis with no previous "renal history" is the confusion that can arise between such a case and one of "arterio-sclerotic kidney" or the "kidney of hypertension". Although in typical cases the distinction can be made, in some cases it is almost impossible to be certain on clinical grounds alone.

Do the various "stages" shew clinically changes in renal function compatible with the pathological interpretations? In acute glomerulo-nephritis there are signs of some degree of impairment of the function of the nephrons. Excretion of end products of nitrogen metabolism, and of water are to some extent impaired, as evidenced by blood analysis and urea range tests. The urine is highly concentrated in an effort to get rid of unwanted substances in the blood stream. The blood pressure is often raised on account of the glomerular obstruction, and to increase the filtration rate.

When we come to the "Second stage" of subacute glomerulo-nephritis we see a remarkable change from the/

the previous picture. There is a slight diminution in urinary output but otherwise the kidney appears to function normally. The non protein nitrogen, urea, creatine etc. of the blood are present in normal amounts. Urea range tests give a normal figure. The oedema and chloride retention are coming to be regarded as extra-renal phenomena. It is difficult to see how a high blood cholesterol can be attributed to the renal lesion.

In the "third stage" of chronic interstitial nephritis we again get evidence of failure of the nephrons. The various end products of nitrogen metabolism begin to accumulate in the blood. The kidney has lost its adaptability. It can no longer concentrate the various constituents of the urine when necessary, and in consequence has to secrete a large amount of urine of low concentration and specific gravity. This impairment of function, which may be slight at first, goes on until the patient becomes "uraemic" if he survives that long.

The sequence of events in the various stages as regards the function of the kidneys can be summarised by saying, that, in the "first stage" function is impaired; in the "second stage" the tide turns and function is almost normal; whereas in the "third stage" we swing back to impairment of function which is permanent and progresses to a fatal termination.

A/

A strange sequence, surely, when we think of the interpretation put upon the pathological changes in the nephrons.

Before we can answer the question asked at the beginning of this section as to whether the clinical aspect is in agreement with the pathological interpretations it would be helpful if we could acquire any knowledge regarding "subclinical" attacks of acute glomerulo-nephritis. If sub-clinical attacks do occur then much of the clinical manifestations of Bright's disease will fit in with the "three stage theory", although as we shall see not completely. If sub-clinical attacks do not occur then it can no longer be possible to regard the theory as entirely correct.

Although, Boyd has said that "absolute proof" of "subclinical" disease "cannot be furnished" it was felt that a trial might at least be made. Such an investigation manifestly cannot be made in hospital practice. But it was felt that in general practice there was some opportunity offered to detect the elusive and much invoked sub-clinical nephritis. So we will now turn to the investigation and its results.

THE INVESTIGATION.

Bearing in mind the aetiological role played by the streptococcus in acute nephritis, it was decided to examine at varying intervals the urine of patients suffering/

suffering from acute streptococcal infections of the throat. The fact that there is often a latent period of one or two weeks between the throat infection and the onset of clinical symptoms of acute nephritis has led many to believe that the nephritis is an allergic response. This meant that the urine of each patient had to be examined at several intervals. It was, of course, impossible to examine every specimen passed from the onset of the throat infection until 3 or 4 weeks afterwards. In fact, as might be expected, it was difficult to obtain as many as three specimens from every patient.

The plan decided upon was as follows:

Each patient complaining of a "sore-throat" received a general clinical examination and also

1. A throat swab was taken and sent for culture to determine if the cause of the condition was the streptococcus and if so which type.
2. The urine was examined for "albumin", red blood cells and casts; the last two by means of microscopic examination of the deposit.
   (a) during the attack of "sore-throat".
   (b) one week after cessation of throat symptoms.
   (c) two weeks after cessation of throat symptoms.

Unfortunately local conditions prevented the first step being carried out after the first three cases. It was then decided to include in the series only/

only cases which occurred during epidemics of acute tonsillitis (which are usually streptococcal) and those which had the typical clinical appearance of a streptococcal tonsillitis.

It was possible to obtain a specimen of urine during the attack of tonsillitis in every case investigated. In many cases the second specimen was also forthcoming, but only in 23 cases was it possible to get patients to cooperate to the extent of furnishing three specimens at the required dates.

No useful function can be served by giving separate accounts of the 23 cases. A few examples as listed below will serve.

M.C. Female, 14 years. Acute onset of "sore-throat". General malaise and pyrexia. Examination of throat showed acute follicular tonsillitis, fauces congested. Also uvula and soft palate. No elevation of blood pressure. Throat swab gave growth of Haemolytic streptococci. Treated by sulphanilamide. Urine was negative throughout period of investigation.

Mrs M.A. 41 years. Acute onset of "sore-throat". History of repeated attacks of "sore-throats" with "quinsy" a year ago. Tonsils, fauces, uvula and soft palate swollen, red and congested. Peritonsillar bulging present on the right side. Cervical adenitis present on both sides. Throat swab gave growth of haemolytic streptococci. Treated with/

with sulphanilamide. Urine "negative" throughout.

J.L. Female 20 years. Acute onset of "sore-throat". History of repeated "mild" attacks of "sore-throats". Pyrexia and general malaise. Tonsils and fauces swollen and congested. Cervical adenitis present. Throat swab gave growth of haemolytic streptococci. Treated with sulphanilamide. Urine"negative" throughout.

J.W. Male, 36 years. Acute onset of "sore-throat". Tonsils, fauces, uvula and soft palate, red,congested and swollen. Seven days after onset sudden lumbar pain, colicky in nature. Pain not repeated; no cause found. No specific therapy instituted. This patient's urine was repeatedly examined and was "negative" on every occasion.

Mrs McM. 42 years. Acute onset of "sore-throat". Tonsils congested and swollen. Some general malaise. No specific therapy instituted. Urine "negative" throughout.

R.W. Male 28 years. Acute onset of "sore throat". History of repeated attacks. Last attack 6 weeks ago. Both tonsils and peritonsillar tissue swollen and congested. Right tonsil exuded pus. The eyelids were "puffy" and the pulse "hard"

(B.P. 130/92). The urine was smoky. "Albumin" was present in considerable quantity. Microscopic examination deposit showed numerous red blood cells. No casts were seen.

Unfortunately this patient had to be sent to hospital and passed from my care. The hospital case sheets shew that he suffered from a typical acute glomerulo-nephritis.

The remaining cases are mere repetitions of the uncomplicated cases already cited. None of the remaining cases necessitated treatment by specific means. They all showed normal urines on each occasion that they were examined. The long list of "defaulters" never showed any abnormality in the urine.

So much, then, for the actual investigation. What conclusions can be reached?

In the first place it is eminently possible that none of the series contracted "sub-clinical" acute nephritis, if we assume for the moment that it exists. The series is far too small for one to be dogmatic. It should be noticed, however, that three of the above cases, (and many more in the complete series) gave histories of repeated attacks of acute tonsillitis. Eight gave a history of a previous attack within the last seven weeks. It is in such cases particularly that one would expect a "clinical" or "sub-clinical" acute/

acute glomerulo-nephritis to follow. Actually one of these cases developed obvious clinical signs of nephritis as already described in the examples given.

Again, it is possible that urinary signs of sub-clinical nephritis were present between the times of urine testing or after they were finished. This objection could only be obviated completely by testing every specimen over a considerable period. Limited to three specimens it was felt that the times chosen were the most likely to show any abnormality if any developed.

The institution of sulphanilamide therapy in three cases was undesirable from the point of view of the investigation but was considered necessary, or at least advisable, in these particular cases. The institution of such a specific therapy might prevent the onset of renal complications. On the other hand such therapy might have resulted in a haematuria from resultant crystallization in the urinary tract, which would have led to confusion in the interpretation, if the "arrow-head" crystals had not been found in the urine.

The answer to the question regarding whether "sub-clinical" acute nephritis exists or not cannot be definite from the present investigation. But it cannot be <u>common</u>. What evidence there is would suggest that, even after repeated attacks of acute tonsillitis,

sub-clinical/

sub-clinical nephritis does not occur.

So far, then, we have no positive clinical evidence, to support the view generally put on the pathological findings. Although I am aware that the progressive "first", "second" and "third stage" view is not universally accepted, I shall refer to it as the "accepted view" as it appears to be the one most widely held. We will now turn our attention , in critical attitude and with more exactness, to this view.

CRITICISM OF THE "ACCEPTED VIEW".

Let us first consider the change from "first" to second" stage. The microscopic pathology shows a lesion which would appear to be progressive as we pass from the former to the latter. As one would expect, in the "first stage" kidney function is impaired to a variable degree depending upon the severity of the lesions in the nephrons. It varies from slight degrees of impairment up to total impairment with uraemia and its concomitant features.

In the "second stage", however, renal function is much improved and renal function tests seldom show impairment. Some authors describe cases with impaired renal function and even true uraemia occurring. This is regarded by most observers to mean that the case has now progressed to the "third stage" or has suffered a superimposed acute attack. Fishberg has described/

described this stage as one of compensated renal hypofunction. Renal function is little impaired and the patient does not die of uraemia. How then are we to account for this "improved kidney function" in the second stage of a progressive disease of the nephrons? A possibility is that many nephrons completely escaped and others suffered minor damage during the acute stage. In this way a sufficient number of nephrons might be left to account for the "compensated renal hypofunction". Richards has shown that in the frog's kidney all the functional elements of the kidney are not functioning at the one time, but rather that they alternate i.e. there is a large reserve. If then a diffusible toxin is circulating in the blood only the active glomeruli will be affected. Thus a large margin might escape. These nephrons could then clear the blood of nitrogenous waste products, as we see does happen in the "second" stage. But, if this is so, where are these spared nephrons during the acute stage? Why cannot they "take over" from the damaged nephrons and maintain normal kidney function? It might be that the inactive glomeruli spared at the time of attack by the toxin, remained inactive during this stage - possibly a defence mechanism. Perhaps arteriolar spasm, which is thought by many to play an important part in acute nephritis, keeps these glomeruli inactive. With the cessation of the acute stage

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and the toxic process these glomeruli might now become active and renal function once more be restored whereas the damaged glomeruli might be repaired as in the case of cure, or continue to function as best they can with the resultant albuminuria etc. of the "second stage".

Examination of specimens does not uphold this view. Very few glomeruli are normal in the second stage, and tubular degeneration is everywhere abundant. Although the glomeruli appear to show an advancement of the lesions seen in the first stage, they cannot seriously obstruct the blood flow through them, or perhaps one should say, to all parts of the nephron, otherwise, on account of the diffuse nature of the lesion, there would be suppression of urine to some degree, raised blood pressure and accumulations of nitrogenous substances in the blood.

It has been maintained that the obstruction to blood flow through the glomerulus is the cause of the tubule downfall. This view must, however, be considerably modified if not entirely abandoned.
For one reason Oliver and his associates have demonstrated, as has previously been mentioned, by microdissection and wax reconstruction, that many tubules present in "third stage nephritis" are aglomerular. Yet they have defied destruction. For another reason, Homer Smith in a review of normal renal circulation points/

points out that there are direct arterial connections with the peritubular plexus. These connections arise both from the intertubular and sub-cortical arteries and also from an occasional small twig - a branch from the afferent artery to the glomerulus. Furthermore, Spanner suggests that the arterio-venous anastomes found in the kidney provide another possible channel whereby the tubular capillaries can receive blood if the circulation to the glomerulus is blocked. Gregerson writes as follows: "Deeper in the cortex.... many of the efferent arteries may not subdivide immediately but take a straight course into the medulla where they form capillary networks of elongated meshes around the straight segment".

From the above observations we see, then, that the vessels of a glomerulus need not supply their own tubule in the deeper parts of the cortex, and that there is direct circulation to the tubules which short circuits the glomerulus.

Presumably, because of these facts it has lately been suggested that the circulating toxin has, by the time the second stage has been reached, damaged the glomerular membrane to an extent which allows it to pass through to the tubules. This would suggest that the tubules reabsorb some of the toxin. This seems to me to be a most unlikely state of affairs. The kidney as an excretory organ is not likely to reabsorb/

reabsorb toxins through its tubules. In view of the alternative circulation it would seem that the said toxin could reach the tubules directly.

This postulation of the toxin escaping through the damaged glomerular membrane is surely a change of ground. A continuous toxaemia seems to have entered the arena, whereas previously it was maintained that second stage and subsequent changes all depended upon the first stage changes resultant from the acute attack. If we are to deal with a continuing toxaemia why do the pathological characteristics change so? Why does renal function improve?

That the first stage is essentially an obstructive glomerulitis with renal impairment and compensatory hypertension is beyond doubt. But that these are the essential lesions "which are destined to influence the whole course of the disease from its inception to its fatal termination" (Boyd) cannot be true when we consider the vascular supply to the tubules and the state of renal function and the blood pressure in the second stage.

McGregor contends that the hyaline fibres formed within the capillaries of the tuft in the first stage become increased in quantity and size until the whole glomerulus is hyalinised by the time the third stage is reached. If this is to be regarded as a process of repair of destroyed tissue - similar to scarring - then it is a phenomenally long process. In fact it

is difficult to believe that an attack of "first stage nephritis" with its attendant lesions could lead to all the tissue changes seen in later stages produced over such a long period, (20-30 years sometimes) and with so many remissions as judged by performance of renal function. This aspect appears to have led to a further change of ground - namely that the kidney is subjected to repeated attacks over a number of years. This means that the third stage is the end picture of numerous acute attacks. This would seem to be more plausible but where does the "second stage" fit into such a scheme?

Another aspect to consider is why do some cases apparently progress from the acute first stage and others clear up completely? If the initial lesions in the kidney were destined to influence the whole course of the disease producing the terrible second and third stages surely all cases would progress in that fashion. Yet we know that what clinically appears to be a very severe case often subsides leaving perfect renal function in its wake. This fact certainly suggests the hypothesis of a continued intermittent assault on the kidney parenchyma by some toxin, in those cases which progress.

Again, there is no positive evidence to show that "subclinical" attacks of acute glomerulo-nephritis occur. Certainly there are mild cases of acute nephritis. Cases where there is little more than a transient/

transient puffiness around the eyelids and the passage of urine darker than normal, lasting perhaps two or three days, might not come under medical attention. But surely patients would remember such a phenomenon when asked directly.

Cases of acute nephritis followed by latent interval before the onset of second stage nephritis present another problem. Here again the latent interval may be characterised by completely normal function and blood pressure and we are asked to believe that progressive changes are going on in glomeruli leading to their obliteration as functioning units with subsequent degeneration of the tubules!

The evidence for the fact that a "second stage nephritis" follows directly upon and is attributable to a "first stage nephritis" seems to be slender. Account is taken only of the fact that clinically such a sequence sometimes occurs, and that the glomeruli in the "second stage" show proliferative changes which could be an advancement of the "first stage" changes. The remarkable tubular degeneration could not be ignored so it was blamed on the glomerular changes without a thought for the normal anatomical facts. On such unsure ground it seems has been built up this theory of Bright's disease. No attention is paid to the functional aspect of the problem, or it is brushed aside on the grounds of imperfect existing knowledge of normal kidney function.

It is a mistake to regard the glomerulitis present in the "first" and "second stages" as necessarily different stages of the same process. The changes in glomerulus are not in any way pathognomonic. They merely show the changes that take place when a glomerulus is subjected to an irritant. Slight variations depend on the intensity of the irritant. Hence an "acute glomerulitis" and a "subacute" or "chronic glomerulitis" is possible.

Focal embolic nephritis which occurs in subacute bacterial endocarditis is freed from suspicion of being a "stage" in Bright's disease and yet the essential lesion is a glomerulitis. True it is not diffuse, only relatively few glomeruli are attacked. There is a leucocytic infiltration of the affected part of the tuft suggesting a suppurative character, but there is proliferation and desquamation of visceral epithelium of the tuft. The diseased loops become adherent to the capsule, and if the patient lives long enough, the affected glomeruli become fibrosed. The glomerulitis here is not very different from the glomerulitis of the "first" and "second stage". Now Bell suggests that the lesion is not embolic but consists of hyaline fibres, identical with that of Bright's disease, which obstructs the lumen of the capillary loops affected. (It is pointed out that few loops of a glomerulus are affected and so tubular changes are not seen!) So we/

we see that the changes characteristic of glomerulitis can be due to different irritants.

One might also mention that late syphilitic nephritis, which is very rare, produces lesions in the glomeruli (glomerulitis) and tubules identical with those of "first stage nephritis".

Consideration of these facts makes one wonder why the "glomerulitis" of subacute parenchymatous nephritis should be regarded as evidence of pre-existing acute nephritis. There seems to be no histological grounds for it at all.

And what of Lipoid Nephrosis? This condition is characterised by the nephrotic syndrome and a great tendency to complete recovery. Pathologically there is marked lipoid degeneration of the tubular cells and no apparent glomerular changes. The condition is not common and the favourable prognosis makes pathological study scanty. Adherents to the "Accepted Theory" maintain either that such a condition does not exist or that slight glomerular changes, similar to those of Bright's disease, are present if carefully looked for. They offer no explanation for the tubular changes occurring with such slight glomerular lesions other than the development of hyper-permeability of the glomerular capillaries which allows the causative agent to pass through to the tubules and exert its toxic effect there.

In/

In "the kidney of the toxaemia of pregnancy" the chief changes again are tubular. There is marked degeneration of the epithelium of the proximal convoluted tubules. Fatty changes are present and there may be a deposit of cholesterol ester. There are also glomerular changes but these do not seem to constitute a "glomerulitis". The changes are swelling and thickening of the walls of the capillary loops but no proliferative changes. The afferent vessels to the glomeruli may show diffuse hyperplastic sclerosis.

In this condition there is no elevation of blood urea or non protein nitrogen. The urine contains an abundance of "albumin", and granular and hyaline casts. The blood pressure is raised above normal to a varying degree. Apart from this latter feature the condition bears a resemblance to Lipoid nephrosis and "second stage nephritis" both as regards ability to excrete nitrogenous waste material, and the prominent tubular changes. The "kidney of pre-eclamptic toxaemia" and lipoid nephrosis give us examples of conditions arising de novo and having many features in common with "second stage nephritis".

In the experimental field it has been possible to Produce a "nephritis" by certain chemical poisons e.g. mercuric chloride, chromates etc. The changes produced are more in the nature of a "nephrosis"; there are/

are intense degenerative changes in the tubular epithelium while the glomeruli are relatively normal. Here again we have evidence of toxic action directly on the tubules. Those who deny the existence of primary tubule degeneration in lipoid nephrosis and subacute glomerulo-nephritis, explain this by saying that the poisons in question, which are crystalloids, pass through the glomerular membrane and exert their toxic action on the tubules whereas toxic colloids are held up at the glomerulus and exert their toxic action in the glomerulus. Tubular degeneration is secondary to the glomerular lesion which results in passage of the toxic colloid to the tubules, and vascular occlusion. In lipoid nephrosis, however, there is no evidence of crystalloid toxin being the cause of tubular degeneration, and it is certain that the renal (and other) lesions of pre-eclamptic toxaemia are due to a colloid toxin. Again in some infective conditions such as diphtheria and typhoid the kidney may be affected. The toxins in this case produce a degenerative change of the tubules without a primary glomerular lesion.

We see, then, that tubular changes due to circulating toxins can occur without necessarily producing visible glomerular damage. It is not necessary to have glomerular damage - producing both circulatory obstruction and increased membrane permeability - to bring about tubular degeneration, for as we have seen/

seen, blood and any circulating toxin can reach the tubules without first traversing the glomerular capillaries.

To summarise what has been pointed out so far, we may take cognisance of the following facts:

1. That kidney function improves when the case passes from "first stage to second stage" which is against a progressive lesion of the nephrons initiated by the "first stage".

2. That the tubular degeneration of "the second stage" is not due to the obstructive glomerular lesion, as the tubules have an adequate blood supply of their own. For the same reason a circulating toxin can reach the tubules without having to pass through a glomerular membrane of increased permeability (although this may play a part.)

3. That proliferative changes of the "capillary endothelium and capsular epithelium designated "glomerulitis" are in no way specific of Bright's disease, but may occur in other conditions (e.g. syphilis and focal embolic nephritis).

4. That tubular degeneration may occur with little in the way of glomerular changes (lipoid nephrosis and pre-eclamptic toxaemia), or without any visible glomerular changes ("nephrosis" of diphtheria, typhoid,) and acute <u>secondary</u> syphilitic nephritis.

Consideration/

Consideration of these facts shows that the evidence for regarding subacute parenchymatous nephritis as a direct sequel of acute glomerulo-nephritis is anything but conclusive. The observation that clinically cases of acute nephritis progress to subacute nephritis is hardly evidence when it is realised that the majority of cases (some 75-80%) do not. The change of renal function from one of impairment to one of compensation is hard to fit in to such a hypothesis although a possibility has already been considered. The main evidence offered by the morbid histologist that the glomerular lesion of the one condition is but a further stage of the other must be refuted when we consider the non-specificity of the "glomerulitis".

So much, then, for the change from "first" to "second stage". The link between the two seems to be severely strained if not broken.

In the "third stage" the microscopic picture shows complete loss of normal renal architecture. Many nephrons have disappeared and there is a replacement fibrosis with small round cell infiltration. This picture, again, is not specific. Indeed it is the picture one would expect after total destruction of the nephrons, whatever the cause. It can be regarded as a stage of healing. We see this picture in chronic glomerulo-nephritis ("third stage") and also/

also in "the kidney of essential hypertension". There are differences between the two - chiefly differences of distribution of the lesions. This is to be expected as in one case the nephrons have degenerated as a result of diffuse toxic changes while in the other the degeneration has been due to gradually diminishing blood supply. A similar picture results of nephron degeneration with fibrosis and small round cell infiltration in a kidney damaged by hydronephrosis. Arteriolo-obstruction plays a part in all these cases.

The round cell infiltration present in cases of chronic glomerulo-nephritis might be taken as indicative of chronic irritation. We know that these cells must play an important part in chronic inflammation, but what that part is we do not know. Collections of these cells are often seen in areas of repair also. It has been suggested that they may play a "scavenging" role, but one would have expected large mononuclear cells to be present if any phagocytosis was necessary. Others regard them as necessary for the formation of fibrous tissue.

The question whether this stage represents true repair or low grade irritation is to some extent artificial, for there can only be repair if there is present a stimulus such as low grade irritation.

The above picture, then, can result from destruction of nephrons and as such might be expected to follow/

follow either the "first stage" or "second stage nephritis" if the nephrons have suffered sufficient damage. Signs of a previous "glomerulitis" indicates that it is the end result of toxic change and not one which is primarily vascular.

This stage of Bright's disease is associated with impaired renal function. Blood urea and non protein nitrogen accumulate in the blood to varying degrees depending upon the extent of nephron degeneration and secondary vascular obstruction.

This "third stage", then, both from the point of view of function and histological change, could follow from either acute or subacute nephritis. In acute nephritis there may be recovery. This may ensue from resolution of the affected nephrons so that they return to normal, or it may be that the number of nephrons damaged is small. These nephrons may degenerate and disappear with resultant changes characteristic of the "third stage", but the large reserve of unaffected nephrons are ample for restoration of normal renal function.

In the "second stage" also, there is the possibility of resolution of the lesions, or if the nephrons degenerate completely one would expect the picture of "third stage nephritis" to develop - both the histological picture and the functional picture.

"First stage" and "third stage nephritis" have features/

features in common which suggest that they really are "stages" of one condition. But what of the so-called "second stage"? It presents renal lesions, but they cannot be fitted in to the process seen in other stages. It presents also a picture of normal blood pressure, raised blood cholesterol, of marked generalised oedema, and lowering of plasma proteins with inversion of the normal albumin globulin ratio. These latter features can hardly be assigned to any renal lesion. Even the lowered plasma proteins with inversion of the albumin-globulin ratio cannot be due to the large loss of albumin in urine for they are present on occasions before the gross albuminuria exists, and also may show marked improvement whilst there is still severe loss of albumin in the urine. Many of these features of subacute nephritis are coming to be regarded as extra-renal phenomena.

Consideration of these facts suggests that subacute glomerular nephritis has a different aetiology and is a different condition from that met with in the acute stage.

The above criticisms must be completely answered before one can agree completely with the theory of the progressive nature of Bright's disease. Otherwise some other theory must be formulated. The chief "bug-bear" is the nephrotic "second stage". How to associate a normal blood pressure and improved renal function/

function with the histological findings, if the interpretations of these findings are correct, seems to be an unsurmountable problem. The raised blood pressure of acute and chronic glomerulo-nephritis is regarded as a compensatory mechanism. Yet in subacute glomerulo-nephritis, when, it is said, the glomeruli are even more obstructed than in the acute stage, the blood pressure is normal and compensation of renal function is almost complete.

It seems to me that there is another possible theory of Bright's disease, which explains more than the "Accepted View" does. It is not, however, complete and does not account for many of the known phenomena.

Before turning our attention to a consideration of an alternative view of Bright's disease, it might be pointed out that there is a tendency among many present day observers to swing away from the "accepted view". This is reflected in the consideration of repeated, or continuous toxic assaults of the kidney as previously mentioned. Working in the field of "hypertension" R.W. Scott shows a tendency to break away from the original Bright's theory. In the same field A. Rae Gilchrist says: "The frequency of chronic glomerulo-nephritis as a cause of hypertension is difficult to estimate, but as a sequence of Acute Bright's disease of sufficient intensity to be recognised/

recognised clinically, chronic nephritis is uncommon." (The italics are mine).

An Alternative View.

If we look at the morbid histology of typical cases of the three types or "stages" of nephritis without any preconceived ideas or bias, we recognise certain broad features.

In acute nephritis we see a picture of "glomerulitis" which is obviously an acute process. We may see some slight degree of tubular damage but not much. This again suggests a short, sharp, toxic action not sufficiently prolonged to have much effect on the tubules.

In the "second stage" nephrotic type, there is again a "glomerulitis". This glomerulitis shows no congestive or exudative element which we see in acute nephritis. All the glomerular changes are of a proliferative nature which from comparative pathological studies of other organs, indicates a subacute process; a response to an irritant of milder intensity than that operating in acute Bright's disease. The tubular changes this time are marked. The changes are not inflammatory, they are purely degenerative. This, again, suggests a fairly low grade toxic action, for although the degeneration is widespread it is not sufficiently severe to prevent normal tubule function.

In the "third stage" the picture obviously presents/

presents either healing and repair, or a degenerative reaction to a still milder irritant of longer duration, that is, it may be a chronic process.

These observations would suggest that the terms acute, subacute, and perhaps chronic, nephritis were the best, and actually reflected the underlying pathology. From this point of view, it is theoretically possible for any of the three types to arise de novo, if the toxic irritant is of corresponding intensity. Also it is possible for intermediate types to occur.

On studying the pathology of these conditions one is struck with a certain amount of similarity between them and acute yellow atrophy, subacute yellow atrophy, and healed yellow atrophy of the liver. The difference in the case of the liver, between the acute and subacute processes is merely one of intensity of the irritant and the tempo of the reaction. Similarly in nephritis, I think there is much evidence to support the view that we are dealing with a parallel process.

Let us, then, apply this aspect to the course of nephritis as observed clinically. Acute nephritis is the result of a relatively severe toxic process and as such can obviously lead to death. This result will ensue if sufficient nephrons are involved and this reaction is of severe degree. Cure may result, if the number of nephrons permanently damaged is relatively slight, or if the inflammatory process is less severe and /

and allows of resolution.

What, then, might be asked of the cases which are seen to "drift on" and display the features of sub-acute glomerulo-nephritis? In acute nephritis ending in death, the toxin produces its maximal and lethal effect before it can be eliminated or neutralised. In a case ending in cure, this toxin is eliminated or neutralised before it has had time to produce its maximum effect. The phenomenon of a case passing directly from acute to subacute nephritis can be explained by imperfect elimination or neutralisation of the toxin. Furthermore the production of this toxin may be continuing and if it is only partially neutralised it can exert its "subacute irritative effects" over a long period.

As illustrative of this I might cite two cases that occurred in hospital. Two children of nearly the same age and both females were admitted to the medical ward within a day of each other. Both suffered from a moderately severe acute glomerulo-nephritis, and gave a history of a "sore-throat" about a fortnight previous to the onset. They were both sent into hospital immediately by their doctors and had received no previous treatment. On examination they both seemed to be suffering from an equal amount of kidney damage. Within a fortnight one of the children had recovered completely and her renal function tests gave normal figures/

figures. The other child remained ill. Although blood ceased to be passed in the urine there was still albuminuria, oedema and raised blood pressure. She progressed in this way for some months. The albuminuria became intense and the oedema massive. The Blood pressure returned to normal. She gradually came to present a typical picture of subacute glomerulonephritis. What factor determined the progress of this child's "nephritis",and yet allowed a comparable case to recover?

Examination of the throat of the child which recovered quickly showed no abnormality, but the throat of the other child showed a chronic tonsillitis with pus exuding from the crypts. This was the only possible factor that could be discovered. With some trepidation she was transferred to a surgical ward for a tonsillectomy on the advice of Stanley Graham. The result was dramatic. Within a few days the oedema and albuminuria diminished. By the time a month had passed she was fit for discharge with normal renal function tests.

According to Stanley Graham (personal communication) it is by no means rare for a subacute glomerulonephritis associated with chronic tonsillitis to improve or actually clear up after tonsillectomy. The process here must have been one of continued milder toxaemia following an acute one, which allowed the/

the "acute glomerulitis" to subside to a subacute lesion. Removal of the source of toxin apparently allowed a certain amount of resolution to take place.

Then, we have to consider the case of acute glomerulo-nephritis which becomes apparently cured, but after a latent period of weeks, months or even years, develops subacute glomerulo-nephritis. Here, the acute phase is cured by neutralisation of the toxin. After a latent period another toxaemia occurs. This toxin may be low grade from the start and give rise to a subacute response, or it may be that it is of the same intensity as before, but that the neutralising mechanism of the body has partially lapsed, and therefore produces imperfect neutralisation. This results in a low grade toxaemia. The latent period in many cases is strongly suggestive of this. It is known in other fields that immunity mechanisms may begin to wane after a stimulating dose of toxin. If this negative phase becomes complete, another stimulating dose may reproduce the whole process again, but if the immunity mechanism is only <u>partially</u> depressed, another stimulating dose may have no effect in increasing the amount of antitoxin. This results in only partial neutralisation of the toxin.

From the above we can see how a case of acute nephritis may be cured, may end in death, or progress directly or after a latent period, to subacute nephritis.

If/

If we regard the "third stage" as one of repair it is obvious that it can result from either a previous acute or subacute nephritis. It is difficult to see, however, how a diffuse third stage nephritis could result from a single acute glomerulo-nephritis. If the lesions were so widespread and intense as to cause such a degree of degeneration, death would occur before there was time for "third stage" changes to occur. It is quite possible, however, to visualise repeated acute attacks leading to an end picture of "third stage nephritis", and this process may be operative in those cases of repeated acute glomerulo-nephritis. It is by no means uncommon to see a case of "chronic interstitial nephritis" have a superimposed attack of acute nephritis.

Cure of subacute nephritis can also occur depending upon the extent and intensity of the damage, provided the aetiological toxin is dealt with adequately. If this detoxication does not occur, then, a slow degeneration will take place with coincident fibrosis and a picture of "third stage nephritis" will result. For this to occur one would expect a prolonged toxaemia possibly waxing and waning.

Cases of subacute nephritis may show a latent interval, when renal function is adequate, before they pass on to the "third stage". There is a possibility here of the affected nephrons being completely degenerated while a healthy "reserve" continues to function/

function during the latent interval during which there is no assault on the kidney by toxin. These remaining healthy units may be subsequently destroyed by fresh toxic assaults - possibly less intense - and also by vascular disease. How great a part the latter plays in chronic nephritis is difficult to assess.

The fact that a case of chronic interstitial nephritis tends to progress towards complete renal failure suggests that it is in truth a chronic nephritis, due to a still milder intensity of irritant. If it were, merely, a stage of healing or repair, one would expect the renal function to stay at a given level. It must not be forgotten, however, that this repair process is associated with vascular occlusive processes thought to be secondary to the compensating hypertension. This vascular occlusion may, therefore, lead to degeneration of erstwhile relatively healthy renal units. In this way a vicious cycle is set up - compensatory hypertension leading to vascular occlusion and further damage.

If this stage is a true chronic nephritis, then the possibility of its arising de novo must be kept in mind. If the toxin concerned were of low enough intensity this might occur. Cases of chronic nephritis with no previous history of nephritis do occur, but it is difficult to differentiate these cases from arterio-

arteriosclerotic kidney of hypertension.

We see, then, that depending upon the intensity of the irritant acute glomerulo-nephritis or subacute glomerulo-nephritis may arise independently from one another. We see also how an acute case can progress directly or with a latent interval to a subacute nephritis due to change of intensity of the irritant. Whether the "third stage" represents repair, or a mixture of repair and chronic irritation it is still impossible to say, probably the latter is nearer the truth.

In the foregoing discussion the term "toxin" has been used in a non-specific sense. Acute glomerulo-nephritis is thought to be due to a streptococcal exotoxin. It may be that subacute nephritis is produced by another toxin with an entirely different aetiology, or it may be that many different toxins can act in this way, as the toxin of diphtheria, typhoid and syphilis can apparently produce this condition.

It is more probable, however, that the majority of cases of the various types of Bright's disease constitute a reaction to the same toxin in varying "doses". The majority of cases of acute Bright's disease recover because the toxin is neutralised. In the small number of cases that either die or change their characters to another type, the immunity re-

actions/

reactions are probably at fault producing no antitoxin, or deficient amounts. Similarly in subacute cases arising de novo there must be impairment of production of antitoxin from the start. Instead of a failure of production of antitoxin being the cause, it may be failure of some other part of the immunity mechanism. In order that an antitoxin can unite with and thereby neutralise its specific toxin, blood complement must be present. Now, it has long been known that blood complement is low in nephritis. The recent work of Kellett and Thomson shows that serum complement is low in cases of acute glomerulo-nephritis during the first four weeks. This is regarded by some as being due to the nephritis in some way, but it might be that it plays a big part in the aetiology. A fresh attack on the kidney while the blood complement was low might well lead to imperfect neutralisation, with the result that although the kidney would not suffer from a large dose of toxin, it would suffer a moderate dose, which would evoke a subacute renal response. A characteristic of subacute glomerulo-nephritis is a tendency for the patient to succumb to some intercurrent infection. The dropsical peritoneum or pericardium is liable to become infected, and the respiratory tract is frequently attacked with the production of bronchitis or pneumonia. This liability to infection is usually assumed/

assumed to be due to the fact that devitalised oedematous tissues have a poor resistance. The oedematous tissues of a cardiac origin do not seem to be so prone to infection, however. Might not the cause be due to an impaired immunity mechanism, which in the first place allowed the subacute nephritis to arise?

In subacute nephritis there is a lowering of the plasma proteins. This is chiefly due to a fall in serum albumin, but nevertheless, serum globulin is diminished also. Now, antitoxins are closely associated with the globulin fraction of the plasma proteins, and it might well be that this lowered serum globulin results in the formation of antitoxin in reduced quantity. There seems to be little doubt that the lowering of the plasma protein, both albumin and globulin, is not solely dependent on the loss through the kidney. It has already been pointed out that the amount of albumin excreted by the kidney cannot alone account for the low level of that substance in the blood, and further, that the serum proteins may rise, while the albuminuria persists to the same degree. There must be some failure of synthesis of plasma proteins, with which may be associated a failure in antitoxin production. This failure in plasma protein production is regarded as being secondary to the renal lesion in some way, rather than primary. If this is so a vicious cycle may be set up. For the nephritis

to/

to become established, there is a relative failure of the immunising process, perhaps due to a low blood complement. The deficiency in the synthesis of plasma proteins subsequently may lead to deficiency in anti-toxin production which will tend to perpetuate the process.

Whatever view one adopts of Bright's disease the correlation of function of the diseased kidneys with the histological features is difficult. It is easy, in a broad way, to understand the changes in function which occur in acute and chronic glomerulo nephritis. In subacute nephritis it is more difficult.

If it is true that this condition arises sub-acutely and independently it is perhaps easier to visualise compensatory mechanisms taking place, than if it is regarded as a further and more marked phase of the acute disease.

In this condition the kidney succeeds in excreting the end products of nitrogen metabolism and this it does without any rise of blood pressure. We saw earlier how this might possibly come about by means of a healthy reserve. Against this, however, was the widespread appearance of the lesions. It has been maintained that the obstruction to the circulation of the blood through the glomeruli is even greater than in the acute stage and that many are consequently bloodless. How then does renal function take place with/

with a normal blood pressure? Circulation through the glomeruli must be less impaired than is thought for renal function to take place so adequately. The albumin in the urine is supposed to be due chiefly to loss of serum albumin through the damaged glomeruli. Even with a reserve of healthy nephrons maintaining kidney function, a fairly good circulation must still be possible through the diseased glomeruli to allow of the abundant albuminuria observed.

The possibility of aglomerular function must also be kept in mind. As previously mentioned Oliver has shown that this apparently takes place in chronic glomerulo-nephritis. It may be that in subacute nephritis the tubules are able to become adapted to function without glomeruli. Nitrogenous waste products could certainly reach them through their "direct" circulation, as could the causative toxin. In this way the tubules, although showing some degree of degeneration might be able to carry out renal function without a compensatory rise in blood pressure. One cannot see how a colloid of large molecular weight like albumin could escape directly into the tubules unless the degenerating tubular epithelium is more permeable than normal, and capillary endothelium is damaged. Some degree of albuminuria, it is true, can be expected to originate from the degenerating tubule cells, but this in itself would be insufficient to account/

account for the total amounts of protein excreted.

One feels, therefore, that tubule excretion alone is an unlikely possibility. It may be, however, that it plays a part. Probably two processes are at work. Circulation through the glomeruli must be better than is often supposed and give rise to most of the albuminuria. Free circulation to the tubules with active secretion on their part might account for the fairly good renal function and normal blood pressure. That the damaged tubules are still capable of executing their normal function is evident. If tubular function is depressed experimentally by cooling or by phlorizin poisoning tubular function ceases. This leads to glycosuria for the tubules fail to reabsorb the glucose filtered off in the glomerulus. The fact that glycosuria does not occur in subacute nephritis shows that, although there are anatomical signs of damage and degeneration they are still capable of a good degree of function.

If the above process does operate in subacute nephritis it must be admitted that it could take place equally well in both the "Accepted View" and in this alternative view. If the tubules can adapt themselves to function without their glomeruli, this process of adaptation would take some time. Whether the condition is due to an advancement of acute lesions or whether it is due to toxin of moderate intensity, there would be/

be plenty of time for such an adaptation to take place. If, however, the tubular degeneration were due to a poor blood supply secondary to glomerular obstruction, such a function on the part of the tubules would be difficult to imagine.

Another factor to consider as a possible cause of renal function being performed at a normal blood pressure is the lowered colloid osmotic pressure of the blood. The effective filtration pressure in the glomerulus depends upon a number of factors and may be expressed as an equation -

$$Pf = Pg - (Pop + Pc)$$

where Pf is filtration pressure, Pg is the glomerular capillary (hydrostatic) pressure, Pop is the plasma colloid osmotic pressure and Pc is the pressure resisting filtration through the membrane - pressure of the capsular fluid. The plasma colloid osmotic pressure is reduced in subacute nephritis due to the fall in plasma proteins (chiefly albumin) and this in itself would allow filtration to occur at a lower glomerular capillary pressure (Pg.). Against this, however, we have the thickening of the capsule and capillary endothelium which would lead to an increase in the value for Pc. If the obliteration of circulation through the glomeruli is as marked as is usually supposed, one would imagine that the raised value for Pc would more than counteract the lowered value for Pop. This would tend/

tend to throw us back again to the possibility of tubular function being the explanation. Moreover, in the normal kidney the glomerular capillary pressure exceeds the plasma colloid osmotic pressure by a large margin (Winton), so that a fall in the latter pressure would not effect a great fall in the former.

Let us for a moment turn our attention to the question of tubular function in the aglomerular kidney. Several species of fish provide examples of aglomerular kidneys. In these fish, the tubule of the kidney is the homologue of the proximal segment of the renal nephron in mammals. "The similarity in function of other homologous structures wherever they occur among vertebrates suggests that the proximal segment of the mammalian tubule possesses, at least potentially, the same functional characteristics as the aglomerular tubule" (Gregersen). Experiments on the renal function of such fish (e.g. goosefish) show that the tubule is capable of excreting water, urea, creatinine etc. Such an aglomerular kidney cannot, however, excrete glucose, sucrose, inulin etc. This aglomerular kidney functions by the act of <u>secretion</u>. Evidence for this is shown by the fact that the maximum secretion pressure may exceed the aortic blood pressure.

If then the kidney of subacute glomerular nephritis becomes adapted so that aglomerular tubular function occurs, we have an explanation for the normal clear-

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clearance from the blood of nitrogenous waste products occurring with a normal blood pressure. In this case the glomeruli could be completely obstructed and functionless. It is more likely however that both processes play a part - glomerular function and aglomerular function by tubules alone.

That tubular excretion in mammals can occur has been proved by experiments with phenol red in the case of the dog. It was calculated by Marshall and Vickers that the amount of diffusible dye (part is combined with plasma proteins) brought to the kidney is insufficient to account for its rate of excretion, even on the assumption of maximal blood flow through the glomeruli. Sheehan confirmed these observations in the dog, and found that in the rabbit also that phenol red is excreted by the tubules.

Surely, then, some such similar mechanism is possible in man. If a subacute toxic process impairs the glomerular function, a corresponding compensatory action on the part of the tubules might occur. If the glomerular lesions resolve, on removal of the toxin, then nephron function could revert to normal again.

In view of the above observation that tubular function in the aglomerular kidney of fish, is totally unable to remove glucose from the blood, it would be interesting to carry out a series of blood sugar curves in cases of "the nephrotic syndrome". If tubular function/

function (of a similar nature as in the fish) occurs to any great degree one would expect a delay in its excretion, with a corresponding rise in blood level above the normal range.

Perusal of the foregoing paragraphs shows that the alternative view offered does not by any means explain all the features of Bright's disease. But it does explain the clinical course of the disease better than the "accepted view". It attempts also to take in the functional aspect of the problem. As we have seen it is the "second stage" nephrotic type that provides the biggest problem. The possible explanations of the better renal function observed in this type have been enlisted above. These attempted explanations, if correct, do not invalidate the "accepted view", but it would seem more probable that such adaptations might take place in a subacute process arising independently, rather than in a progressive degenerative process of the nephrons. This alternative view interprets the histopathology more accurately, for it has been shown that none of the features can be regarded as pathognomonic for one and the same process, but rather that they are non-specific responses to any type of irritant.

SUMMARY.

A brief résumé of the pathological aspect of Bright's disease is given. The interpretation usually put on the pathological findings is that the various types of Bright's disease represent different stages of one continuous process which is initiated by the primary glomerular lesions in the first or acute stage. Hence the use of the terms first, second and third stage nephritis. The continuous process is usually regarded as a progressive degeneration of the renal elements brought about by the obstruction to blood flow through the glomeruli.

The clinical course of Bright's disease is briefly reviewed. It is pointed out that only a minority of cases pass through the three stages or types. Subacute or "second stage" nephritis is often encountered apparently arising independently. The explanation of this phenomenon by assuming a pre-existing "subclinical" acute nephritis is discussed. The functioning power of the kidneys in the three stages or types of Bright's disease is described. It is pointed out that acute glomerulo-nephritis and chronic glomerulo-nephritis are associated with impairment of excretion of nitrogenous end products by the kidneys and that the blood pressure is raised, while in subacute glomerulo-nephritis excretion of nitrogenous/

nitrogenous end products is adequate, and the blood pressure is normal.

An investigation is described which attempts to establish the presence or absence of a "subclinical" acute glomerulo-nephritis. The limitations of the investigation are pointed out. No evidence was found to favour the presence of such an entity.

The view that Bright's disease is a condition which inevitably progresses from the acute stage through the subacute to the chronic stage, or ends in cure after the acute or subacute stage, is criticised. It is pointed out that the fact that renal function improves when a case passes from the acute to the subacute type is not in keeping with the view that the change is due to a further progression of damage to the nephrons initiated in the acute phase. That the tubular degeneration which is so marked in subacute glomerulo-nephritis, is due to vascular obstruction of the glomeruli is shown to be false. It is demonstrated that the tubules have their own direct blood supply which is quite adequate even although glomerular circulation is abolished entirely. If the acute stage initiates a chain of events which leads inevitably to a small granular kidney with failing function, why do not all cases show this progression? A point is made of the fact that the glomerulitis seen in Bright's disease is not pathognomonic for that condition. It is a non-specific response which

can result from a variety of stimuli or toxins of varying intensity. Such glomerular changes are seen in focal embolic nephritis, syphilitic nephritis, in diphtheria and typhoid etc. That tubular degeneration can occur with little or nothing in the way of coincident glomerular changes is evidenced by such conditions as lipoid nephrosis, nephroses due to chemical irritants etc.

An alternative view is suggested. The micropathology of the various types of Bright's disease are regarded as reactions which vary in tempo in accordance with the intensity of the irritant, so that acute, subacute, and to some extent chronic, reactions take place. The similarity between the process and that which occurs in acute, subacute yellow atrophy, and healed yellow atrophy of the liver is mentioned. In this way cases of acute and subacute glomerulo-nephritis can arise de novo. It is suggested that the response evoked in the kidney (the type of nephritis) depends on the intensity of the circulating toxin. The toxin may be the same for all types of Bright's disease or may differ. Chronic focal sepsis would appear to play a part in the aetiology of some cases of subacute glomerulo-nephritis.

The method by which the toxin intensity may vary is discussed. Partial breakdown of immunity mechanism is suggested as a cause, and is linked with the low blood/

blood complement and proteins observed in some cases of nephritis.

The possibility of aglomerular tubular function in sub-acute and chronic glomerulo-nephritis is mentioned. This is not regarded as being the sole mechanism by which the kidneys function but may well play an important part.

CONCLUSIONS.

From these reflections it is felt that the "accepted view" rests on very slender evidence, namely, that some cases do progress through the various stages, and that the glomerular changes can be traced through these stages. As we have seen there is nothing pathognomonic about "glomerulitis". It can result from a variety of causes.

The known facts would appear to be explained by the alternative view more satisfactorily. The evidence suggests that subacute nephritis is due to a toxin of less intensity than is encountered in acute nephritis, and as such may arise independently or follow an acute attack. Chronic glomerulo-nephritis is probably a stage of healing with perhaps some mild irritant action superimposed, and is therefore a sequence of repeated attacks of acute glomerulo-

glomerulo-nephritis, or of subacute glomerulo-nephritis.

The necessity for more numerous and extended investigations into the question of "subclinical nephritis" is appreciated.

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