The clinical course of Bright's disease

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THE CLINICAL COURSE OF BRIGHT'S DISEASE

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INTRODUCTION

The study of the course of any disease seems to me the primary method to acquire an understanding of the disease. I feel that a working knowledge of the subject of Bright's disease is of immeasurable value to the general practitioner or specialist. With this reason in view, an extensive survey of the literature was made and this paper prepared.

Only monographic style of literature was consulted and placed in the bibliography. Reference to the bibliography is made in the body of the theme by number system. Many articles were surveyed which were not listed in the bibliography as they were of no value to the restricted scope of the subject.

There has been very little work done on the clinical course of Bright's disease from its beginning to its termination. However to Van Slyke et al in their recent publication in medicine, I owe much for my system of construction as their method of presentation was followed and added to as I deemed necessary. With this basis a comprehensive study was made and presented. Many of the finer, more delicate clinical laboratory observations were omitted for an attempt to restriction in this massive subject. It is plainly evident that much must be omitted to cover such a subject within these pages.

The classification of the disease has been restricted to that of Adie's published in 1925 which is the simplest and yet most inclusive.

In this paper, for the sake of brevity, the subject matter has been carefully restricted to the clinical course of Bright's disease only. Etiology, pathology, and treatment enter in only incidentally but have been kept in mind throughout.

There has been no original case studies made and presented; the paper is one of general survey in an attempt to accumulate data of the different phases, separating the phases, and showing by this accumulation what seems to be outstanding and usual features of the type of the disease. Consequently there are no arguments submitted and no theories attempted to be proved; merely submitted facts.

There are three types of Bright's disease discussed which, according to Adie's, includes all forms of nephritis. In the order in which they have been taken up they are:

1- Hemorrhagic (glomerulonephritis)
2- Arteriosclerotic (nephrosclerosis)
3- Degenerative (nephrosis)
THE CLINICAL COURSE OF BRIGHT'S DISEASE

The study of Bright's disease dates back to 1836 when Richard Bright made his first report on the study of albuminuria as a result of kidney disease. Since then there has been a growing work in the subject which has resulted in descriptions of several varieties of the disease and very many classifications. But understanding a disease found in one organ as the kidney, it is hard to appreciate numerous types of the disease existing singly and distinctly by themselves. So in this paper the three main types will be discussed, each one inclusive of it's supposedly described Sub-Typhes. In general there are three forms of Nephritis understood as separate entities of the same disease but even these are apt to over-ride each other's boundaries.

These are:

1- Hemorrhagic (glomerular) nephritis
2- Arteriosclerotic (nephrosclerosis)
3- degenerative (nephrosis, lipid or amyloid)

The object of this part is to formulate the clinical course of nephritis from the development to the terminal state. The fundamental understanding of a disease depends on a knowledge of its course. Etiology and treatment considerations will be avoided.

The most outstanding work of modern times that has given us a working basis on the subject of nephritis is the classical work of Volhard and Fa hr, 1912-1918. At present there is being produced an immense amount of original work at the Rockefeller Institute upon the subject of Bright's disease which promises to add great light to the present understanding of the subject.

For charity and simplicity the course of the disease shall be discussed in this paper separately under the three types named above.

Hemorrhagic or Glomerular Nephritis

Hemorrhagic nephritis is seen first as a rule in the acute stage of the initial form or as an acute exacerbation. It is marked regularly by hematuria, proteinuria, and edema while anemia, reduced kidney function, hypertension, and plasma protein reduction are frequent findings. As will be seen later, the severity or mildness of these symptoms has no relation to the prognosis (3), (4). This statement is immediately seen to contradict the general opinion of physicians.

One of four out comes may be expected:
1- Complete recovery
2- Latency, free of subjective symptoms but retaining some proteinuria
3- Active chronicity ultimately leading to death
4- Death occurring usually within a few weeks from the onset

Does a hemorrhagic case run true to form throughout it's course, or does there occur a migration later into the degenerative or sclerotic types?
The majority of the investigators agree that the former case is true. Adair (3) states that in Bright's disease we are dealing with groups of diseases under the general head of nephritis which are all related but tend to run separate courses.

Adair (1), has pictured this unity of hemorrhagic nephritis with the simple but illuminating diagram of the possible stages in its course:

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  Healed
    Latent
  Acute
  Chronic active
    Terminal
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In the above diagram the nature of the direction lines describes the frequency of the course: the unbroken lines show the most frequent courses and the broken lines each relatively less down to the dotted lines which are very rare.

In the progress of the disease the change into the different stages is never sharply marked. The boundaries are all broad. From one definite stage to another may be days or more usually weeks and months involved.

ACUTE STAGE

It has been mentioned above that the study of hemorrhagic nephritis commences with the acute stage either at its beginning or at an acute exacerbation. In a series of 50 cases in this stage studied at the Rockefeller Institute (3), the usual duration was found to be from 3 to 4 months before passage to one of the other stages. In all cases, except those few passing into the chronic or terminal stages early, improvement occurred within 4 months. Edema was the last objective sign to disappear and the last clinical laboratory sign was proteinuria which often continued months after the patient was subjectively well. Occasionally slight hematuria would be the last sign to leave. Longcope (5), found in a series of 87 cases that in 87% this disappeared in this stage with the lesion healed.

LATENT STAGE

Usually the acute stage tends to pass over into latency in 3 - 4 months unless the patient is fated to pass into the chronic or terminal stages from the acute. (3). During the period of latency the patient is subjectively well. Adair (1) states he has observed a great number of patients ... the latent stage enjoying apparently perfect health up to ten year's time. However there is always present an abnormal number of red blood cells and red cell casts. The very slow progressive destruction of glom-
eruli is met with by a steady compensatory hypertrophy. (1)

If the blood pressure was high in the acute stage—which is the usual case—it now drops to normal or near normal.

Recovery may now take place or, after years have passed, the stage may change to that of chronicity or terminal. In those latent cases of years standing the general course is to the healed stage if the cause is removed—usually a streptococcal focus. As the diagram shows it is rare for a latent stage to be reached from an arrested chronic state, the usual result being terminal.

Active Chronic Stage—
This stage corresponds to the chronic hemorrhagic parenchymatous nephritis and the nephrotic glomerulonephritis.

In this stage there is chronicity of symptoms. The function of the kidney is diminished, — the area excreting power being used as an indicator. Van Slyke (3) found that in this stage the area excreting power remained above 20 per cent of normal. When lower than this the case passed into the terminal stage.

From the acute onset if improvement does not take place, or the terminal stage reached within 4 months, the patient passes into the chronic active stage characterized clinically by general weakness, malnutrition, edema, and always hematuria and albuminuria. The blood pressure is usually elevated. If the hypertension persists, and especially if the diastolic pressure rises, some degree of retinitis becomes manifest. (4) Blood studies will show a hypercholesteremia and low plasma protein, the abnormality of which seems to be in direct proportion to the amount of edema.

If receiving a case in this stage for the first time, it is difficult to distinguish it from the degenerative type (nephrosis) as all findings are alike except the hematuria and this may be so scant as to require very careful and sensitive methods to discover it. (3) But the history of previous infection, hematuria, and some period of latency should clinch the diagnosis of glomerular destruction. (4)

In this active chronic stage there is degeneration taking place as in nephrosis and Addis (2). has shown that both conditions represent degenerative kidney lesions, the difference being that the hemorrhagic type has an additional pathological factor,—glomerular inflammation. It is important to know and appreciate the similarity of the course of this stage with nephrosis as the prognosis of the two tends to opposite outcomes. The most usual outcome of the chronic stage of hemorrhagic nephritis is death in the terminal stage from 6 months to 2 years, while in true nephrosis the prognosis should be favorable for recovery or death by some intercurrent infection. (1), (3), (4). This description of the course of the chronic stage is discouraging in appearance, but in view of the fact that Longcope (5) had shown in a large series of cases not more than 15 per cent of the cases of acute hemorrhagic nephritis pass into this stage, we should support optimism about the disease.

Terminal Stage—
This stage is usually reached through the chronic active stage but some cases are so rapid in their course that it is reached through no intermediate stage. In this stage appears the uremic syndrome.

The signs of degenerative diseases may be present but usually they gradually disappear during the terminal stage and the patient falsely appears improving. Addis (1) explains this as follows: As one after another of the inflamed glomeruli become completely disabled and fibrosed so that urine no longer flows down their tubules, fewer red cells and pus cells come from the shrunken kidney, and blood casts are hard to find. Edema lessens because the albumin excretion is thus diminished and as a result the plasma protein brought back toward a normal level. This process may take place during many months and upon this basis Van Slyke (3) modifies this stage by calling this the pre-terminal phase. During this phase the urea excreting power remains above 20% of normal and the N. P. N. content of the blood only slightly raised. The blood pressure may or may not be elevated. But when the urea excreting power once falls below 20% normal, it is a pathognomonic of ensuing uremia. (3) Now according to Addis peculiar large, clear, flat casts, "renal-failure casts" (6) are always found and are of the same significance as the urea excreting level of below 20% normal.

It was found at the rocheller Institute (3), that once this final phase of the terminal stage was reached, death came invariably either through uremia (most commonly) or by intercurrent infection within one year's time.

CLINICAL OBSERVATIONS

Urea Excreting Power-

According to Addis' work in 1923 (7), there is a definite relation of the excreting power of the kidneys in producing urea to the amount of secreting tissue present. He finds that with the amount of this tissue constant that the amount of urea excreted in the urine in 1 hour bears a direct proportion to the amount of UCC of blood drawn at that time. In some of his recent work (1), he states that when 1/3 or less of the secreting tissue remains there relationships remain and the patient inevitably progresses to uremia.

Van Slyke (3), after studying his series of 50 cases gives us some positive statements about prognosis. It was shown earlier in this paper that the apparent severity of acute onset had no bearing on the prognosis of later stages. He states that the essential for a good prognosis is that sometime within 4 months from the acute onset that the urea excretion, if below normal, should commence a steady climb toward normal. The normal may never be quite reached but the prognosis may still be good in that normal persons are found with a urea excreting power of 70% of the average. But in his cases he found that if this climb did not commence, or show signs of doing so, that all cases went into the chronic active and terminal stage.

In the chronic active stage the function may rise but always temporarily.
The prognosis is uremia in a few months, or in some cases, a few years. The terminal stage is reached when the function is below 30% normal and uremia occurs when at 5% or less.

Hematuria:

This is the most characteristic clinical finding and yet the most invaluable for prognosis. From the work at the Rockefeller Institute, Addis, Longcope and others we see that unlike ura excretion in no stages can we prognosticate on the hematuria found. Usually there is macroscopic hematuria at the onset of the disease. In the latent stage hematuria may persist this markedly and yet all other findings disappear while in the chronic active frequently only by the finest sediment examinations may there be found red cells. This again shows how easily hemorrhagic nephritis might be diagnosed nephrosclerosis if the case is first seen in the chronic stage unless a history of hematuria is obtained. But we may say that hematurias really indirectly governs the prognosis as it classifies the disease.

Blood Pressure:

In the acute stage there is usually an elevated blood pressure which is one of the early symptoms to disappear. Here again is a symptom in the acute stage which bears no light as to what the future holds. But there is a usual course of hypertension over 150 mgm of mercury for 4 - 6 months. However Van Slyke has observed that in his series some cases that progressed rapidly to the terminal stage never showed an elevated blood pressure while other cases developed hypertension which persisted into the latent stage to disappear only months after every other sign was gone. Yet Moschowitz (4) states that he has observed that though the acute symptoms are valueless for prognosis, if severe albuminuria associated with hypertension does not disappear within two months the prognosis is unfavorable.

Addis, Moschowitz, Van Slyke and others all agree that though we are accustomed to think of hypertension in glomerulonephritis, it is not always present and especially in the latent stage the blood pressure usually remains normal. If there is hypertension no complaint as the patient invariably states he feels quite well.

It has been taught that glomerulonephritis acquired and disappearing in childhood is the underlying basis for hypertension nephritis to develop later in life. When the renal origin of hypertension was baulked this was good logic if not proved. But since the subject of hypertension is releasing nephritis as it's cause this logic fails and this requires proof which is lacking. In studying the pathogenesis of glomerular nephritis Moschowitz states he can find no basis for this assumption (4). Brench and Linder (9) have shown by autopsy that in six out of seven dying in uremia with hypertension that there was arterio-sclerosis to account for the hypertension.

It is found that in the chronic active stage about 30% show hypertension the severity of which had no relation to early hypertension.

In the terminal stage there is less hypertension because before reaching uremia many are found to show a great drop in blood pressure. By this time most cases show retinal changes if an albuminuria has
One may say in conclusion of this important symptom discussion that
though hypertensive occurs in most but not all cases in the acute
stage, it is usually but not always absent in the latent stage; in
the late stages it carries a bad prognosis as do the other symptoms.
There is no evidence that childhood hemorrhagic nephritis without
continuity of symptoms is a case of later hypertensive. At no other stage
does the presence of hypertensive have a definite prognostic significance
concerning the renal function: only that of hypertensive itself with
it's possible end results via the circulatory system.

Plasma Proteins

No reduction in plasma protein in the acute stage carries a good
prognosis (3). Likewise in those cases maintaining a relatively
high level in the acute stage the prognosis is relatively good
(Linder and Lungsgaard (10), (11). These men found that those cases
which fell below 5.5 per cent protein volume of plasma progressed to
the chronic active and terminal stages. They also found that in
cases reaching the latent stage there was no tendency for protein
drop. Their work shows that the chronic and terminal stages develop
in cases with low plasma protein. As the terminal stage is reached
there is a marked tendency for the protein per cent to increase,
(3), (10), (11). This was explained early in the paper by the con-
traction of the kidney which likewise diminished the albuminuria
and the other urinary findings. So it appears that unlike the urine
secretion function, the hematuria, and hypertension, the plasma
protein content has a direct prognostic value on the case.

Proteinuria—

Here again is a symptom of the acute stage bearing little or no
relation to the severity of the disease. In Van Slyke's series of
cases all that showed small amounts became cured but likewise his case showing the most loss of protein in the urine became cured
in a few weeks. The deaths came, however, from those showing an
intermediate amount and the maximum amount but in these there was
no relation of morbidity results to the amount of proteinuria. From this
it seems we might be privileged to be optimistic in a case showing
only minimal proteinuria.

The duration of proteinuria is variable. It may last from
2 weeks to 5 months in the early cured cases. In the latent form it
usually persists and here the amount bears no significance. In those
cases passing into the chronic active stage there is no marked change
in the protein escape but it never is scant as in the arteriosclerotic
form.

In the terminal stage the proteinuria may remain unchanged, it is
never increased, but often decreased and not infrequently decreases to
To quote Epstein's hypothesis on the causation of edema in this form of nephritis: (12) "The loss of protein incurred by the blood serum through the continuous albuminuria causes a decrease in the osmotic pressure of the blood, which fact favors the absorption or imbibition and retention of fluids in the tissues." From this it would indicate that the discussion of edema should be associated with the thought of the plasma protein and proteinuria findings.

The most recent work by Van Slyke and fellow workers at the Rockefeller Institute shows evidence to support this hypothesis exactly with the exception of the acute stage.

In the initial period of the acute stage we see massive edema and acites as the rule, yet the plasma protein is not early lowered even though copious amounts of albumin pass thru the kidneys. So there must be some other reason, perhaps toxemia, affecting the circulatory system at some point the capillaries to allow this edema. This edema is always tam orary if plasma protein is not reduced soon. In the acute stage edema persisted regardless of diet if the protein of the plasma was lowered.

In the latent stage where the protein is above the critical level of 5.5 per cent no edema is found.

In the chronic active stage the tenacity to edema is an outstanding finding. As was previously stated, most all of these show a plasma protein below 5.5 percent and an albumin below 2.5 percent. In all these cases edema is found. (3). There are some few who, on a salt free diet and reinforced treatment, will show only a tenacity to edema and the correspondence between this and the plasma albumin is practically uniform. (3)

As was stated above, in the terminal stages the plasma protein deficit is much less common than in the chronic active stage (Adams (1); Van Slyke (3); Meschisnitz (4); Epstein and Van Slyke both find that the edema is correspondingly less. It is to be stated now that in any case in the terminal stage, that the cardio-vascular system has a tendency to give way and may very likely account for edema at this time.

We may say now that with the exception of the initial stage that the edema in hemorrhagic nephritis corresponds to the amount of plasma protein deficit.

Anemia-

The causation of an anemia found in the initial acute stage is probably due to the present hemorrhage (14). There is also found a close correlation between the anemia and the degree of decreased renal function. (3) However cases are many in which uremia is reached with no decrease in
hemoglobin. So we find that this measure is of about the same prognostic value as in the case existing power as described above. The absence of anemia does not mean necessarily a good prognosis.

In the latent stage there is little or no anemia. (1), (3), (14).

In the active chronic stage anemia is usually the course and there is usually a relationship between this and the decreased renal function of urea excretion (3), (14). But here again, there may be cases of poor function with no anemia.

Brown and Roth (14) view anemia in the chronic stage as a result of a general toxemia in which the hemopoietic organs have their function insulted either continuously or repeatedly and as a result the bone marrow becomes hyperplastic and is slow in regeneration of erythrocytes. With the anemia they found a close parallelism of the damage done to the bone marrow, retina and cardio-vascular system. They also found as was found at the Rockefeller Institute that the decreased function of urea excretion usually, but not always, had a direct relationship to the degree of anemia. They have both presented cases with urea excretion less than 20 per cent of normal with hemoglobin between 50 and 100 per cent.

Brown and Roth feel, however, after studying all the blood contents in relation to the anemia that the urea function has the closest correlation.

In all cases reaching the terminal stage through the chronic stage, anemia is present before uremia develops. (1), (3). It is found that with the anemia there is a marked deficit of urea excreting ability, the reverse of which holds more frequently in the terminal than in the chronic stage.

We may conclude then, that anemia ceases a grave prognosis but the maintenance of a nearly normal hemoglobin does not contradict the onset of uremia.

Cardiac Changes-

It has been noticed in the preparation of this paper that there is little to be found concerning cardiac changes in anemcoholic nephritis, yet hypertension is freely discussed. Nevertheless there are some definite changes which was recently shown by Levy (15), in a series of cases and his survey of the literature.

In 1879 Goodhart wrote in Gray's hospital reports, that: "Probably many are quite alive to the occurrence of sudden death from ventricular dilation in acute nephritis, but it is not taught as one of the things generally known". This expresses the present day appreciation of the subject.

The remaining discussion on this subject will be based upon Levy's article, (15) Tice, Practice of Medicine, and Oxford Medicine.

It is always assumed that there are to be found cardiac changes in
chronic glomerular nephritis but it is in the acute case where the ignorance lies. The findings are variable but bear a close relationship to the degree of hypertension. Simultaneously, with the advent of hypertension, cardiac changes appear. The acute cases may be divided into three groups. In the first the patient will notice only slight dyspnea, slight orthopnea, and when prone some cyanosis of the lips. In the second more severe group the patient definitely complains of dyspnea, orthopnea, and abdominal distress. An enlarged painful liver is found. Vesicular rales are heard in the long bases. In the third group the cardiac symptoms predominate. There will be found a loud systolic murmur transmitted to the axilla and with this is the usual signs of heart failure. Levy states that in this group patients will be cured for as heart cases with complete overlooking of the cause or with this in mind blood and urine studies may reveal hemorrhagic nephritis as the primary case. He reports two examples of this.

Early X-ray studies of the heart and carrying them on through the acute stage have shown that with the onset of hypertension there is cardiac dilatation to a small or great degree and this is first in the right heart. Death may come suddenly with severe rapid developing hypertension and heart failure due to dilatation.

As the hypertension strain and toxic insults continue through the acute stage, the heart will commence to compensate through muscular hyperplasia. This is always favorable as an aid is now being affected for the riddance of the blood toxins and the cardio-renal edema.

In the latent stage a heart which gave definite symptoms during the acute stage, usually gives no complaint and a slight enlargement or none at all will be found.

In the active chronic stages there is nearly always hypertrophy, It is always found in cases with persistent hypertension. There may or may not be a faint murmur heard. The sounds are loud and of good quality. The apex has is usually pronounced. In all, the heart gives a picture of compensation by hypertrophy with the apex to or slightly beyond the mid-clavicular line. The enlargement is not so great as in the essential hypertension cases.

In the terminal stage heart failure may or may not be associated with uremia. However dilation of the right heart is usually found. Many cases in the terminal stage die before uremia develops from an heart failure.

Retinal Changes—

Eye ground changes are not nearly as frequent in the acute stage as in the chronic. However cases of albuminuria retinitis are not uncommon. There may be a true papillitis and a true albuminuric retinitis occur in the acute stage, especially those with hypertension. Those cases going into uremia form the acute stage may frequently, develop an amblyopia of uremia without any retinal changes (May; Diseases of the Eye)

In the latent stage the only eye ground findings are those which
may have developed in the acute stage (Tics; Practice of Medicine, Oxford Medicine).

In the chronic stages retinitis is a very likely prognosis. Some degree of disturbed vision is to be expected in most all cases. There may be blindness if the macula is affected.

In the terminal stage, the prognosis is still worse for retinal changes. Blindness frequently occurs with uramia (May; Diseases of the Eye).
ARTERIOSCLEROTIC BRIGHT'S DISEASE or NEPHROSCLEROSIS

CHRONIC INTERSTITIAL NEPHRITIS

Arteriosclerotic Bright's disease (Addis) or nephrosclerosis (Volhard and Fahr) is commonly and lightly spoken of as chronic interstitial nephritis. This latter name should be discarded—it means nothing.

The discussion on Hemorrhagic Bright's disease has been lengthy due to the bizarre form and multiplicity of characteristics that accompany the disease. That is a disease usually commencing in childhood and frequently running it's course through the rest of the patient's life. In the arteriosclerotic type we cannot comparatively say it is bizarre in any form; multiplicity of it's characteristics is limited and it is usually a disease of advanced life. Consequently this discussion, due to the necessity of limitation will be proportionately short, but will be accomplished in the same manner as was hemorrhagic nephritis.

Arteriosclerotic Bright's disease is usually thought of as a vascular syndrome. As early as 1872 Bull and Sutton (16) give a fundamental idea which is exactly what we learn today, supposedly from our most recent works. They stated and demonstrated pathologically that the real disease back of what we call chronic interstitial nephritis is a disease of the small blood vessels and that the lesions of the kidney are secondary manifestations.

GENERAL COURSE

Given a case under this classification we find hypertension, cardiac hypertrophy, and slight proteinuria as the outstanding characteristics. Hypertension is the cardinal symptom in all cases and this is the first symptom in all cases. (1), (3), (16). Jameway (12) in conclusion to his studies on nephritic hypertension states in regard to arteriosclerosis that, "Hypertension may arise in primary irritability of the vasoconstricting mechanism from unknown, probably extrarenal causes, which lead eventually to arteriosclerosis. In this type the disease of the kidney is the sequence, not the cause, of the generalized vascular lesion. When it progresses to a condition of extremen atrophy, resulting in the true primary contracted kidney, a renal element may be added to the existing hypertension." To this statement Volhard and Fahr agree in their work which came to light at the same time. Also does Addis (1) Van Slyke (3) and Branch and Linder (3) agree to that statement.

As pointed out by Volhard and Fahr there are two types of this disease, the benign and malignant. (3) In both forms the first clinical sign is hypertension, and the first pathological changes appear to be in the smallest and smallest arteries.

In the benign form the course of the disease continues unaltered to the end which usually comes many years afterwards. The symptoms are practically entirely attributable to a cardio-vascular disease, and death comes from
13- circulatory rather than renal failure. It is in this form that the diagnosis of essential hypertension will be made if the trace of albumin in the urine is over looked.

In the malignant form the course early is like that of the benign but sooner or later a rapid decrease in renal function ends itself to the picture, and death follows, usually in a few months, with symptoms of renal failure frequently accompanied by those of cardiac failure. With this form of death changes in the beginning of the renal insufficiency (Volhard and Fahr (3).

Clinical observations are not made in the study of these cases concerned in this paper until proteinuria is found because until this exists the case is not considered one of Bright's disease. Consequently the course during the initial hypertension stage is not observed. Here also we cannot classify and observe this disease in stages of progress as in hemorrhagic Bright's disease because it is definitely chronic through out it's course and always persists to death.

CLINICAL OBSERVATIONS

Urea Excreting Power-

The urea excreting power is usually normal (1), (3), (17). Volhard and Fahr (17) submit a series of 243 cases of benign form in which 77 per cent had normal excretion and where only 4 per cent were anything more than slightly below normal. In the malignant form this is low in all cases but is variable to the seriousness of the disease as was found analogously in terminal hemorrhagic nephritis. The malignant form is terminal artherosclerotic nephritis. In the benign form the common course is for the urea excreting power to remain good to the end. (17) In conclusion it may be said that the urea excreting power is not disturbed in the majority of cases and is thus of little prognostic value in itself. In the more rare malignant form it is only one of the host of "pre-uremic death" changes to be noted.

Hematuria-

Addie (1) uses the lack of hematuria as a differentiating point from hemorrhagic nephritis. Volhard and Fahr agree that it is exceptionally rare. Van Slyke and others (3) report a few instances but presume it to be a terminal phenomenon.

Blood Pressure-

Hypertension is the cardinal symptom and may be the single symptom and years before proteinuria develops. In the series of cases at the Rockefeller institute (3) the diastolic pressure in all was above 120mm. but these cases were all studied after they were definitely classified as Bright's disease. The systolic pressure usually were 200 mm. and above. Volhard and Fahr report many cases with moderate hypertension as 170 mm. while Mcllroy (17) states early the blood pressure is between 170 and 200mm. and as the course progresses mounts to points of 250mm. and higher as the termination of life is reached. Varying heights may be found in the same case.

In all, we may say that the blood pressure is always high and the prognosis as of chronic hypertension with arterial changes should always be given.
Plasma Protein-

Plasma protein content is always normal. (3)

Proteinuria-

In the benign form, the proteinuria is usually a trace. Upon strict dieting treatment and rest it can often be made to temporarily disappear (16). The patient will pass on to death showing more than a trace only as a terminal thing and not always here. (3), (16), (17), (39).

With the onset of the terminal malignant form the albumin is found to increase greatly. In a sense it indicates the severity of the renal failure but gives no measuring value. (3), (17). As with the diminished urea excreting power this is only one of the many terminal symptoms.

Edema-

Nephritic edema is lacking in this disease. If it is found it is of cardiac origin which of course is not infrequent. (14), (3), (16), (17).

Anemia-

Anemia is not an outstanding finding as might be expected at first. But when we remember that in the benign form this is a non-obliterating disease and that the malignant form comes on suddenly and terminates suddenly, we don't expect this. McLlroy (17) states that often in the benign form there is a polycythemia present but does not attempt to explain this. Brown and Roth (14) in the study of anemia in chronic nephritis state a parallelism between the degree of toxemia and the anemia. Also they found, as have others (14), (17), that the anemia in the terminal malignant stage is never as severe as in the terminal stage of glomerulonephritis. Vain Slyke (3) found only one case in this late stage that showed any remarkable development of anemia. In no occasion is anemia as pronounced a symptom as is found in hemorrhagic nephritis.

Cardiac Changes-

Cardiac changes always develop sooner or later. This needs little discussion as these changes are always expected in chronic hypertensive cases. First there is left sided hypertrophy, the aortic second sound is loud and snappy. Later there is right sided hypertrophy and dilatation. Now there may develop murmurs, arrhythmias, and as the myocardium nears its exhaustion, fibrillation may develop. Cardiac death is now inevitable.

Retinal Changes-

Eye-ground examinations are of great value here in differentiating the benign from the malignant forms. Volhard and Fehr considered it so valuable that they state that with the finding of retinitis we know the
the malignant form has developed. This may be the only early form of differentiation between the two forms. (1?) As the disease progresses in the benign form, arteriosclerotic changes may be the only findings in the fundi; rarely hemorrhages(1?). (May - Diocesis of the Eye) There is gradually diminution to blindness through retinitis of the albuminuric type in the malignant form. This may even develop before proteinuria is found.

Thus we find a basis of prognosis in ophthalmoscopic studies.
DEGENERATIVE BRIGHT'S DISEASE OF NEPHROSIS

Here is a disease, an entity, that one may find widely discussed and argued. There is a multitude of periodical literature to be found on the subject, all of which seems to be in a state of confusion and this confusion apparently maintained by arguments and illustrations concerning the etiology and pathology of the disease. Among all this literature we find very little effort expended upon the study of the course of the disease and yet most all writers agree that nephrosis is an entity as worked out by Hunk, Volhard and Fehr, and Epstein several years ago. (23)

There is good evidence to question this entity as being a type of Bright's disease, (18) but as long as albuminuria is considered significant of Bright's disease, this subject will be classified as such. There is no type of Bright's disease with such chances of being mixed with the other types as with this.

Regardless of arguments as to it's pathology and etiology this discussion shall be presented showing the course of the non-inflammatory degenerative type of Bright's disease as described by Moller, Hunk, Volhard and Fehr, Epstein, Judis, and Van Slyke.

GENERAL COURSE

By degenerative Bright's disease we mean a rare condition in which one finds, as outstanding features, massive edema and anemia, low blood pressure, marked albuminuria with high specific gravity, a urinary sediment rich in casts and a freedom persistently from blood cells, and a kidney that shows essentially a degenerative process of the epithelial cells. Further we find globulin in the urine, absence throughout the course of eye-ground changes (unless complicated), there may or may not be anemia, and there is retention of salts. There is a normal non-protein nitrogen in the blood, an increase in blood cholesterol and lipoids, and a decrease in the total plasma proteins with relative increase of globulin. There is usually a distinct low basal metabolic rate. (18), (21).

This disease appears to follow, or accompany a heterogeneous set of intoxications and infections, frequent among which are pregnancy, toxemia, endocarditis, tuberculosis, and syphilis. In many cases there is no obvious etiology; the event begins insidiously, with without previous noted illness or intoxication.

Death is generally believed to occur extremely rarely by this disease but by intercurrent infection to which the patient is extremely susceptible (13), (19), (31), (23), (34). However, Van Slyke and co-workers present cases showing that uremic deaths are not uncommon. (3)

The above symptoms and findings of the disease may or may not all be found, though usually most of them are. The outstanding constants are: decrease in plasma albumin with relative increase in globulin, and an increase in lipoids and cholesterol; the lack of anemia, hypertension, urea retention and anemia. (1), (13), (21), (22), (23). Van Slyke (3) in his recent work agrees with the first group of constants but finds that any one of these factors that are supposed to be lacking may be found in certain cases sometime during the course of the disease.
Adice (1), (2), (3), so much as the lack of our knowledge at present concerning Bright's disease, classifies nephritis precisely today, even the finding of degenerative forms of epithelial cells in the urine through out the active course of the disease. Thus he states that unlike hemorrhagic nephritis, this disease is not a unity, but is only a convenient term under which to classify all those pathological conditions which may give rise to degenerative processes in the kidney parenchyma. He sums these under six headings:

1 - Those of unknown etiology, which he terms cryptic degenerative. They are seen first presenting cases and the true initial stages in not seen. Here the disease may pass through active and latent stages to complete recovery, or may gradually regress to azotemia and death. This latter progress is not usually believed to occur as many observers state that death comes only by intercurrent disease. But many writers agree with Adice (Service (17), Kaufman and Mason (21), McElroy (25), and Van Slyke (8)). In the active stage the ligamen is high as is the cholesterol and great cases of thyroid extract does not raise the basal metabolism rate. (1), (19), (13).

2 - There are those degenerative diseases with known chemical constitution. The heavy metals, medicinal jaundice are examples. This is acute scarlet fever and the course depends on the extent of tissue destruction. This type is frequently referred to as the necrotizing type by Vollhard and Fehr, Epstein, McElroy and others. If severe enough the termination may come soon through azotemia following oliguria, anuria, and hypertension. In mild cases the albuminuria and azotemia will disappear in a few weeks and leave no subjective or objective findings, yet there is always a lowered renal reserve to be remembered.

3 - Degenerative kidney disease is known to the obstetrician but is not considered so much by the internist as the disease is usually not lived and treated by the obstetrician. Adice states that his study of the cases at Stanford University revealed that as the rule the disease is transitory and may never leave a noticeable impairment to renal function afterwards, but in neglected cases vascular and parenchymal damage may be so severe that azotemia or cardiac death result. Sclerosis may develop following a short course of this disease and in this case the prognosis is worse than in those cases with sudden development of sclerosis. In the latter case the insult to the kidney is not of such long standing. (1)

4 - The toxemia that may accompany any generalized infection is apt to produce a slight amount of cloudy swelling of the kidney and give albuminuria. This is usually transitory with the toxemia but it occasionally happens that the degeneration becomes extreme and there is much epithelial debris, protein, and cast in the urine. This seldom is fatal and usually a cure follow. (1), (2), (19), (23).

5 - Focal infections are seldom associated with anything but minor degree of renal degeneration. (1) However an occasional case is seen that leads to heavy proteinuria and azotemia but the course is favorable with removal of the focus. (1), (2).
This last classification given by Addis are those nephrosis caused by chronic debilitating diseases that were mentioned above and give a similar picture in kidney pathology. The waxy or liquid kidney. The course of this disease is exactly that of the first mentioned cryptic type, (1), (3), (12). It is this type that Munk in 1913 described as liquid nephrosis because of the presence of double refractory lipid bodies in the urine. He claimed that the cause of this disease was syphilis.

It is evident that the subject of non-hemorrhagic Bright's disease is not understood universally with agreement. At present there seems to be a chaotic state of confusion concerning the disease and the study of the course of the disease is based upon much dogma, especially so in Epstein's, classical work. However, the remaining effort on this presentation will be placed upon the clinical observations using the same outline as in the previous two types of case study.

CLINICAL OBSERVAIONS

Urea Excreting Power-

At the Rockefeller institute (3), a series of 10 cases are presented which confirm with the most generally accepted qualities, necessary to classify them as nephrosis. There they found that the urea excreting power was diminished in 5 of those and not only normal in the other two but at times hypernormal. They state that this phenomena is seen in occasional cases recovering from acute hemorrhagic nephritis. It is well to recall that early in this paper it was stated that at times hemorrhagic nephritis cannot be demonstrated as differing from nephrosis aside from the history.

In 5 of their series the diminished urea excretion remained or progressed slowly to worse conditions. This over a period of a few years. Thus with 10 frank cases only 3 regained apparently normal renal function. Three cases passed into uraemia.

McIlroy (33) agrees in many of his findings that unlike common belief urea retention is not infrequent and that uraemic death may be expected in small per cent of cases. Major (32), has found this to be true by clinical observation also. This impresses the writer that there may be more than tubular affection in true nephrosis.

Hematuria-

It is well here to mention again that hematuria is consistently absent in this disease which may be the only means of differentiating from some latent cases of hemorrhagic nephritis.

Addis (1), (2), definitely states that hematuria is invariably absent and for this fact is a most valuable point in diagnosis. No writers argue this point. Van Slyke (3), reports finding it once in one case.

The outstanding findings microscopically, the urine are the tubular casts with epithelial degeneration findings. Suck (33), states double refractory lipid bodies are the characteristic microscopic findings to be expected. There seems to be no opposition to this statement.
Blood Pressure-

Hypertension is constantly absent. No case reports were found stating that it was present in true nephrosis. In the so-called questionable mixed types were the only ones presenting hypertension. (19), (21).

Plasma Protein-

Epstein and Van Slyke state that the study of the plasma protein is of first interest because the albumin-globulin ratio is in direct relation the amount of edema. Not all writers accept this, but it shall be of no further concern in this paper.

Actually the amount of plasma protein is about 6-8 percent and the albumin-globulin ratio about 2-1. (3), (18), (19). A few writers say this ratio may still higher normally. (33), (35). All agree in every article consulted that this ratio is altered with a decrease of the albumin and a relative increase in globulin in every case. Thus Epstein (18) finds in some cases the total protein as low as 4 per cent of plasma volume and globulin as high as 90 per cent of total protein.

Van Slyke et al. (3) reports a case having had an albumin per cent of .8 and completely helpless from edema who in a years time raised this per cent to 3.8 and was leading a sedentary life with no apparent discomfort.

Fifty per cent of the series of cases studied at the Rockefeller Institute (3) which is the largest series found) never showed a total albumin per cent above 3.5 and all of these had heavy persistent edema. These cases were alive at the time of report and were apparently well aside from the discomfort of the edema. Three cases with albumin above that point constantly, passed to the terminal stage and death through intercurrent infection. Apparently, albumin deficit has little relation to susceptibility to intercurrent disease which is an outstanding feature of the disease as before stated.

In the discussion of the plasma protein, Epstein states that in nephrosis there is constantly found an elevated per cent of cholesterol in the plasma with other lipoids. This seems to meet with no opposition by other investigators.

In conclusion we see that though the blood plasma protein is constantly lowered and the ration of albumin to globulin lowered, there is little prognostic value in this knowledge. This condition persists through out the disease and the only definite relationship found between this and other features of the disease is the edema.

Edema-

Edema, Epstein states, is the second outstanding point of interest. There is invariably seen in nephrosis edema, usually in massive amounts at some stages with effusion in all serous cavities.
The edema gives the patient a grayish white color and definite palor. This is not due to anemia. Epstein (13), (24) states definitely that the edema is caused by protein deficit and that raising the protein in the blood reduces the edema. He presents cases to show this. There is little protein found in the edema. Elwyn (2), and Kaufman and Mason (21), attempt to explain this physiologically as well as clinically to be true. Van Slyke et Al (3), agree with Epstein but shows 3 cases where the edema became diminished or disappeared under treatment with no elevation of the protein. However his other cases which developed higher protein concentration, all showed diminished edema.

Epstein's theory of edema and it's course in relation to plasma protein (albumin) seems to sound and is accepted by most investigators. In no article was prognostic significance placed upon edema alone.

Proteinuria

Little discussion is necessary upon proteinuria as all writers agree that it is ever present as long as there is a direct relation to the plasma protein deficit. The amount of proteinuria is variable in cases but is usually tremendous. Kaufman and Mason (21), report as high as 3 per cent of the urine.

Because of the relation of the proteinuria to the plasma protein, Epstein would term the disease "Diabetes Albuminuricus".

Anemia

It is generally believed that anemia is not found in nephrosis. Thus McIlroy (23), states there is no marked anemia unless due to complications. Most writers are not this definite but state anemia is either never or very rarely found in cases of degenerative Bright's disease. But considering the malnutrition and the frequency of prolonged complications, it is hardly possible to conceive of anemia being extremely rare in this disease. Epstein does not make much note of it yet propounds the theory that the disease is purely one of diminished metabolic function. It would seem strange to picture a disease of this type without a certain degree of definite anemia. There is a theory that the hemoglobin may be low due to the dilution of the blood by edema fluids. Brown and Roth (14), have conclusively disproved this. These two men state that anemia accompanies the cardio vascular and retinal changes. We see later these are of less importance.

Van Slyke (3) reports anemia in most all of his cases but attributes it to intercurrent complications in the main. Thus he cites a case with septicemia which developed a hemoglobin of 40 per cent. The patient recovered and the hemoglobin reached 100 per cent in the face of signs of more severe renal degeneration.

There seems to be no impressive satisfactory explanation in the literature why anemia in a true uncomplicated case of nephrosis does not develop when this is so characteristic in the previous two types of Bright's disease discussed. This comparison would favor the theory prevalent at this time that nephrosis is a systemic disease primarily
and not a nephritie. It is apparent that hemoglobin studies are of no value in the study of the course of this disease.

Cardiac Changes—

It is stated in all the literature that cardiac changes are not found in true cases of degenerative Bright’s disease. This is probably the case in true nephrosis but Servier (19) expresses what we should bear in mind in making a prognosis: “Every one understands that kidney disease seldom merges a clear-cut course and that one type of nephritis often merges into another”. As was stated early in this paper we cannot draw clear-cut lines between the types of nephritis as some overlapping is to be found in most cases. However it may be said with much support that cardiac changes are of inferior importance in this disease.

Retinal Changes—

Lack of retinal changes in nephrosis is considered one of the characteristics of the disease. McElroy (17) states that he doubts that any true form of the disease has retinal changes and if retinitis does develop it is due to the disease being a mixed type. Epstein (19) (24), makes light of any retinal findings stating it is very rare if seen at all. However there is accumulating more recent evidence to show that retinitis does occur in degenerative Bright’s disease. Since the “kidney of pregnancy” has been classified under this disease there is no question but what it is seen at times.

Haufman and Mason (31), report that in their 3 cases presented none showed retinal involvement early, but definite albuminuric retinitis was found to develop in the later stages. Van Slyke et al (3), report finding retinal changes in those cases which later went into uremia. These were discussed earlier in the discussion of the area excreting ability. This seems to be enough evidence to point out that given proper factors the retinitis may develop and continue until the patient is definitely on the road to recovery.

Albuminuric retinitis in pregnancy is known to exist by all but apparently is seldom considered under the heading of nephrosis. From May’s text on Diseases of the Eye, we find the statements that the signs and symptoms of this retinitis is like that of other albuminuric retinitis. Detachment is not rare but usually disappears as does the retinitis after delivery. This differs distinctly from any prognosis given to other cases. The occurrence of retinitis is usually in primipara in the later months and it usually clears up with delivery but is more serious in those cases in which it develops early in gestation.

Uremic amблиопия should be differentiated in cases of loss of sight in pregnancy as here there are no retinal changes and the prognosis is good if the patient recovers. The cause of the blindness is cerebral phenomena.
CONCLUSIONS

In studying the literature we find that degenerative Bright's disease is comparatively rare. There are clinical characteristics which are described at the beginning of the discussion. It has been found that many authorities make positive statements concerning the course of the disease. It has been found in preparing this paper that there are many exceptions from to all these statements which have been embodied in this work, and that though there is the clinical entity we cannot be positive in the prognosis of any of our clinical observations.
SUMMARY

This paper has been written with the purpose of accumulating into one theme the clinical course of Bright's disease. There has been no attempt at statistical study in the strict sense of the word nor has there been a confusion of mathematical figures.

More space was devoted to hemorrhagic nephritis than the others solely because it was found that the disease is more bizarre, has the most stages, has the longest course because of usual childhood development, and is the most studied of the types. The Arteriosclerotic type is the most frequent but its course is most constant, and has fewer features and consequently does not demand the same amount of discussion. The degenerative form of nephritis is at present much less understood and agreed upon than the others so much space was required to present comparatively fewer facts than in the others. This is by far the richest form of Bright's disease.

The variations within each of the 3 types of Bright's disease studied are great. A few of the salient features will be given for each type:-

1- Hemorrhagic (glomerulonephritis). An acute onset either healing or improving to an intermediate latent stage to heal from there or progress into a chronic active and then the terminal stage to uremia and death. Death is not the most common outcome. The initial hematuria and edema have no relation to the nature of the prognosis.

2- Arteriosclerotic (nephrosclerosis). An insidious onset with hypertension of the benign or malignant form and with cardiac hypertrophy. Albuminuria retinitis develops after the malignant hypertension results, and cardiac insufficiency with resultant edema is not to develop. Death occurs by cardiac failure, apoplexy or less frequently, uremia.

3- Degenerative (nephrosis). An insidious onset with usually massive edema and marked proteinuria and low plasma protein percent with increased albumin globulin ratio in the plasma. Basal metabolism is usually low. Improvement is indicated by increase in plasma protein and decrease proteinuria. A cure is not infrequent but the patient is very susceptible to intercurrent infection which is the common cause of death. It is true that pure cases may occasionally terminate in uremia.
1. Addison T.
   "A Clinical Classification of Bright's Disease."
   J.A.M.A. 35:163 1925

2. Addison T.
   "The Renal Lesion in Bright's Disease"
   Harvey Lectures 1927-28 33:222

3. Van Slyke, Edgar Stillman, Herbert Muller et al.
   Observation on the Course of Different Types of Bright's disease, and
   on the Resultant Changes in Renal Anatomy.

4. Moschosowitz, Eli:
   "The Neural History of Acute Glomerulo-Nephritis"

5. Longcope, W.
   "The Pathogenesis of Glomerular Nephritis"
   Bull Johns Hopkins Hosp. 45:335 1929

6. Addison T.
   "Renal Function."
   J.A.M.A. 84:1013, April 4, 1923

7. Addison T.
   "Renal Function"
   Arch. Int. Med. 30:376-385 1923

8. Addison T. and Drury D. R.
   "Effect of Changes of Blood Urea Concentration on the Rate of Urea
   Excretion"
   J. Bio. Chem. 55:105 1923

   "Arterio-sclerosis with Hypertension in Chronic Nephritis."
   J. Clin. Inv. 3:193 1928

10. Moore N.S. and Van Slyke D.D.
    "Relationship Between Plasma Protein Content and Edema in Nephritis"
    J. Clin. Inv. 3:337 1928

    "Change in Plasma Protein in Nephritis"
    J. Exp. Med. 39:921 1934

12. Miller A. McIntosh J.F.
    "Excretion of Albumin and Globulin in Nephritis"
    J. Clin. Inv. 4:235 1928

13. Epstein A.A.
    "Edema in Chronic Paranchymatous Nephritis."
14- Brown G.A. and Roth, J.M.
The Anemia of Chronic Nephritis
Arch. Int. Med. 30:17-460 1922

15- Levy, Jesse
The Cardiac Response in Acute Diffuse Glomerulo-Nephritis
The Am. Heart J. 5:277 Feb. 1930

16- Janeway, T.C.
Nephritic Hypertension - Clinical and Experimental Studies.
The Harvey Lectures 1913-13 P. 208

17- Tice, Practice of Medicine
Vol. 2:357

18- Epstein A.A.
Chronic Nephrosis

19- Service, S.F.
Nephrosis

20- Elwyn, R.
The Pathogenesis of Lipoid Nephrosis
Arch. Int. Med. 1926, 35:358

21- Kaufman, J and Mason E.
Nephrosis
Arch. Int. Med. 1933, 35:531

22- Major, R. H. and Helwig F.C.
Clinical and Pathological Studies in Chronic Nephrosis.

23- McElroy, J.B.
Nephrosis
J.A.M.A. 1927, 83:340

24- Epstein A.A.
The Nature and Treatment of Chronic Parenchymatous Nephritis
(Nephrosis)
J.A.M.A. 89:144 Aug. 11, 1927

25- Buck R.V.
The Diagnosis of Nephrosis
N. Eng. J. Med. 201:875-972 Nov. 14, 1929