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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 on understanding of the disease. I feel that a working knowledge of the subject of Bright's disease is of immeasureable value to the general practitioner or specialist. With this reason in view, an expansive survey of the literature was made and this paper prepared.

Only monographic style of literature was consulted and placed in the bibliography. Referance 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 it's 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 Addis' 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 accumilate data of the different phases, separating the phases, and showing by this accumilation what seems to be outstanding and usual features of the types of the disease. Consequently there are no arguements submitted and no theories attempted to be proved: merely submitted facts.

There are three types of Bright's disease discussed which, according to Addis, 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 1838 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 discriptions 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-Types. 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 bounderies.

These are:—

1— Hemorrhagic (glomerular) nephritis
2— Arteriosclerotic (nephrosclerosis)
3— Degenerative (nephrosis, lipoid or amyloïs)

The object of this paper is to formulate the clinical course of nephritis from the developement to the terminal states. The fundimental understanding of a disease depends on a knowledge of it's 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 Fahr, 1913-1918. At present there is being produced on immense amount of ginal work at the Rockefeller Institue 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.

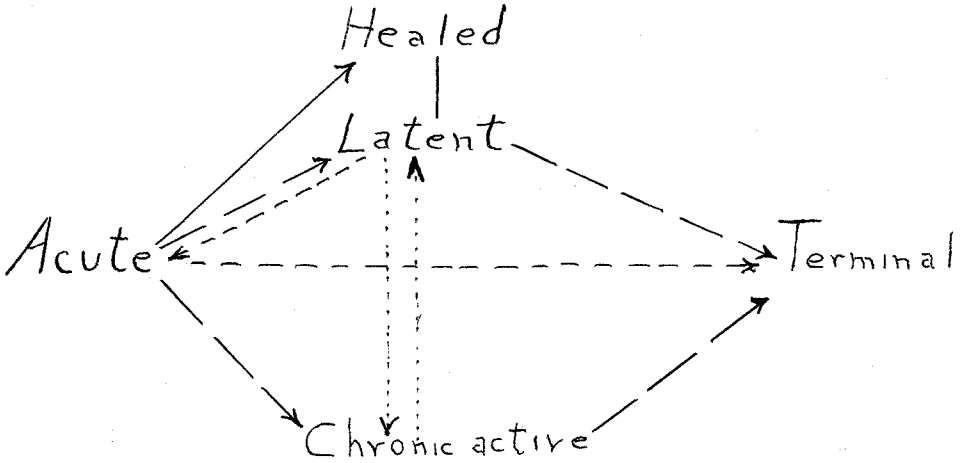
One of four out comes may be expected:—

1— Completer recovery
2— Latency, free of subjective symptoms but retaining some proteinuria
3— Active chronicity ultimately leading to death
4— Death occuring 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. As Addis (2) 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.

Addis (1), had pictured this unity of hemorrhagic nephritis with the simple but illumination diagram of the possible stages in it's course:-



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 it's 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 2 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 occured within 4 months. Edema was the last objective sign to disappear and the last clinical laboratory sign was protienuria 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 67 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 2 - 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. Addis (1) states he has observed a great number of patients in 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 distruction 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 takes 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 streptococcus 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 deminished, -- the urea excreting power being used as an indicator, Van Slyke (3) found that in this stage the urea 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, mal-nutrition, edema, and alwyas 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 protién, 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 cinch the diagnosis of glomerular distruction. (4)

In this acitve chronic stage there is degeneration taking place as in nephrosis and Addis (2). has shown that both conditons represent degenerative kidney lesions, the difference being that the hemorrhagic type has an additional pathological factor.--glomerular inflamation. 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 apposite outcomes. The most usual outcome of the chronic state 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 discription of the course of the chronic stage is discourging in appearance, but in view of the fact that Longcope (5) had shown in a large series of cases not more than 13 per cent of the cases of acute hemorrhagic nephritis pass into this stage, we should support optomision 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 digenerative disease 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 deminished 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 elivated. 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 Rochefeller institute (3), that once this final phase of the terminal stage was reached, death came invariably either through uremia (most commonly)- or by intercurrant infection within one year's time.

CLINICAL OBSERVATIONS

Urea Excreting Power-

According to Addis' work in 1922 (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 urea in 10000 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 uremeia.

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 severety of acute inset had no bearing on the prognosis of later stages. He states that the essential for a good prognosis is that sometime within 4 months form 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 stages.

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 terinal 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 Rochefeller institute, Addis, Longcope and others we see that unlike urea 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 nephrosis if the case is first seen in the chronic stage unless a history of hematuria is obtained. But we may say that hematuria 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 hyper-tension which persisted into the latent stage to disappear only months after every other sign was gone. Yet Moschawitz (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, Moschcowitz, Van Slyke and others all agree that though we are accustomed to think of hpertension 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 is usually of low grade and gives no

It has been taught that glomerulo-nephritis acquired and disappearing in childhood is the underlying basis for hypertension nephritis to develope later in life. When the renal origin of hypertension was believed 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 reguires proof which is lacking. In studying the pathogenisis of glomeulor nephritis Moscheowitz states he can find no basis for this assumption (4). Branch 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 80% show hypertension the severity of which had no relation to early hypertension.

In the terminal stage there is less hypertension because before reaching uremea many are found to show a great drop in blood pressure. By this time most cases show retinal changes if an albuminuria has

persisted with the hypertinsim. (4)

One may say in conclusion of this important symptom discussion that trough hypertinsim 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 caries a bad prognosis as do the other symptoms. There is no evidence that childhood hemorrhagic nephritis without continuity of symptoms is a cause of later hypertinsim. At no other stage does the presence of hypertinsim have a definite prognostic significance concerning the renal function: only that of hypertinsion itself with it's possible end results via the circulatory system.

Plasma Protein-

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 Lunggaurd (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. There work shows that the chronic and terminal stages develope in cases with low plasma protein. As the terminal stage is reached there is a marked tendancy for the protein per cent to increase. (3), (10), (11). This was explained early in the paper by the contraction of the kidney which likewise diminished the albuminuria, and the other urinary findings. So it appears that unlike the urea 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 did his case showing the most loss of protein in the urine become 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 morbid results to the amount of proteinuria. From this it seems we might be privileged to be optomistic 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

a trace (Miller and Mc Intosh (12).

Edema-

To quote Epsteins hypothesis on the causation of edema in this form of nephritis. (13) "The loss of protein incurred by the blood serum through the continous albuminuria causes a dicrease 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 protien and proteinuria findings.

The most recent work by Van Slyke and fellow workers at the Rochefeller 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, effecting the circulatory system at some point the capillaries to allow this edema. This edema is always tem 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 tendancy 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 per cent. In all these cases edema is found. (3). There are some few who, on a salt free diet and reenforced treatment, will show only a tendancy to edema and the correspondance 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 (Addis (1); Van Slyke (3); Maschaiwitz (4); Epstien 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 tendancy 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 is the urea excreting 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 stages 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 continously 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. The, also found as was fo nd at the Rochefeller 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 hemoglobins between 60 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 bears 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 hemorrhagic nephritis, yet hypertension is freely discussed. Neverthe less there are some definite changes which was recently shown by Levy (15), on a series of cases and his survey of the literature.

In 1879 Goodhart wrote in Grey'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 in severity 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. Vesicualr 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 cared for as heart cases with complete overlooking of the cause or with this in mind blood and urine studies may reveal nemorrnagic nephritis as the primary cause. He reports two examples of this.

Early Xray 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 suduenly 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 persistant hypertension. There may or may not be a faint murmur heard. The sounds are loud and of good quality. The apex has its usually pronounced. In all, the heart gives a pictue of compensation by hypertrophy with the apex to or slighty 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 urmeia. However dilation of the right heart is usually found. Many cases in the terminal stage die before uremia developes from an heart failure.

Retinal Changes-

Eye ground changes are not nea rly as frequent in the acute stage as in the chronic. However cases of albuminuric retinitis are not uncommon. There may be a true papillitis and a true albuminic retinitis occur in the acute stage, especially those with hypertension. Those cases going into uremia form the acute stage may frequently, develope 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 (Tice; 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 effected.

In the terminal stage, the prognosis is still worse for retinial changes. Blindness frequently occurs with uremia (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 patients life. In the arteriosclerotic type we cannot comparitively 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 fundimental 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). Janeway (13) 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 conditon of extremem 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 (9) 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 small 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

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 adds 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 with the beginning of the renal insufficiency (Volhard and Fahr(3). retinitis usually appears

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 242 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 arteriosclerotic 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-

Addis (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 phenomena.

Blood Pressure-

Hypertension is the cardinal symptom and may be the single symptom and years before proteinuria developes. In the series of cases at the Rochefeller 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 hypertensions as 170 mm. while McElroy (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.

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), (9).

With the onset of the terminal malignant form the albumin is found to increase greatly. In a sense it indicates the severety of the renal failure but gives no measuring value. (3), (17). As with the deminished 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. (1), (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-debilitating disease and that the malignant form comes on suddenly and terminates suddenly, we don't expect this. McElroy (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 (3), (17), that the anemia in the terminal malignant stage is never as severe as in the terminal stage of glomerulonephritis. Van 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 develope 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. Late there is right sided hypertrophy and dilatation. Now there may develope murmurs, arrythmias, and as the myocardium nears its exhaustion, fibrillation may develope. Cardiac death is now inevitable.

Retinal Changes.

Eye-ground examinations are of great value here in deferentiating the benign from the malignant forms. Volhard and Fahr considered it so valuable that they state that with the finding of retinitis we know the

the maligmant form has developed. This may be the only early form of differentiation between the two forms. (17) As the disease progresses in the benign form, arteriosclerotic changes may be the only findings in the fundi; rarely hemorrhages(17). (May - Diseasis of the Eye) There is gradually diminution to blindness through retinitis of the albominuric type in the maligmant form. This may even develope before proteinuria is found.

Thus we find a basis of prognosis in ophthalmoscopic studies.

DEGENERATIVE BRIGHT'S DISEASE or 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 arguements 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 Munk, Volhard and Fahr, 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 classed 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 arguements as to it's pathology and etiology this discussion shall be presented showing the course of the non-inflamitory degenerative type of Bright's disease as described by Moller, Munk, Volhard and Fahr, Epstein, Addis, and Van Slyke.

GENERAL COURSE

By degenerative Bright's disease we mean a rare condition in which one finds, as outstanding features, massive edemas and anasarca, low blood pressure, marked albuminuria with high specific gravity, a urinary sediment rich in casts and a freedom persistantly from blood cells, and a kidney that shows essentially a degenerative process of the epithelial cells. Further we find globulin in the urine, absence through out 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 chalesteroal and lipoids, and a decrease in the total plasma proteins with relative increase of globulin. There is usually a distinct low basal metalolic rate. (18), (21).

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

Death is generally believed to occur extremely rarely by this disease but by intercurrant infection to which the patient is extremely susceptable (18), (19), (21), (23), (24). 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 cholesteral; the lack of hematuria, hypertension, urea retention and anemia. (1), (18), (21), (22), (23). Van Slyke (3) in his recent work agrees with the first group of constants but finds that any one of those factors that are supposed to be lacking may be found in certain cases sometime during the course or may develope as a terminal find-

ing. Some of Mosher's and Addis's work agrees with Van Slyke's (21)

Addis (1), (2), (3), to which we owe much of our knowledge at present concerning Bright's disease, classifies nephrosis practically solely upon 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 conveinient 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 unkown etiology which he terms cryptic degenerative. They are seen first presenting edema and the true initial stages is not seen. Here the disease may pass through active and latent stages to complete recovery, or may gradually progress to uremia and death. This latter progress is not usually believed to occur as many observers state that death comes only by intercurrant disease. But many writers agree with Addis (Service (19), Kaufman and Mason (21), McElroy (23), and Van Slyke (3). In the active stage the lipemia is nigh as is the cholesterol and great doses of thyroid extract does not raise the basal metabolism rate. (1), (18), (19).

2- There are those degenerative diseases with known chemical constitution. The heavy metals, malaria, jaundice are examples. This is of acute sudden onset and the course depends on the extent of tissue distruction. This type is frequently referred to as the necrotizing type by Volhard and Fahr, Epstein, McElroy and others. If severe enough the termination may come soon through uremia following oliguria, anuria, and hypertension. In mild cases the albuminuria and edema will dissappear 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 short lived and treated by the oostetrician. Addis 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 neglicted cases vascular and paren-chymal damage may be so sever that uremic or cardiac death result. Eclampsia may develope following a short course of this disease and in this case the prognosis is worse than in those cases with sudden development of eclampsia as in the latter case the insult to the kidney is not of such long standing. (1)

4- The toxemia that may accompany any generilized 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), (3), (19), (23).

5- Focal infections are selfom associated with anything but minor degrees of renal degeneration. (1) However an occasional case is seen that leads to heavy proteinuria and edema but the course is favorable with removal of the focus. (1), (2).

6- This last classification given by Addis are those nephroses caused by chronic debilitating diseases that were mentioned above and give a similar picture in kidney pathology. The waxy or lipoid kidney. The course of this disease is exactly that of the first mentioned cryptic type. (1), (3), (18). It is this type that Munk in 1913 described as lipoid nephrosis because of the presence of double refractory lipoid 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 OBSERVATIONS

Urea Excreting Power-

At the Rochefeller 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 deminished in 8 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 7 of their series the deminished urea excretion remained or progressed slowly to worse conditons. This over a period of a few years. Thus with 10 frank cases only 3 regained apparently normal renal function. Three cases passed into uremia.

McElroy (23) agrees in many of his findings that unlike common belief urea retention is not infrequent and that uremic death may be expected in a small per cent of cases. Major (22), has found this to be true by clinicla 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 consistantly 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 in the urine are the tubular casts with epithelial degeneration findings: Buck (25), states double refractory lipoid bodies are the characteristic microspopic 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.

Normally 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 ration may be still hgigher normally. (23), (25). 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 totoal protein.

Van Slyke et al (3) reports a case having had an albumin per cent of .9 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 2.5 and all of these had heavy persistant 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 intercurrant infection. Apparently albumin deficit has little relation to susceptability to intercurrant 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 (18), (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), agrees with Epstein but shows 3 cases where the edema became deminished or disappeared under treatment with no elevation of the protein. However his other cases which developed higher protein concentration, all showed deminished edema.

Epstein's theory of edema and it's course in relation to plasma protein (albumin) seems to be 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 the disease is active and bears 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 McElroy (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 concidering 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 deminished 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 develope when this is so characteristic in the previous too 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 nephritis. 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 Service (19) expresses what we should bear in mind in making a prognosis: "Every one understands that kidney disease seldom pursues 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 develope it is due to the disease being a mixed type. Epstein (18) (24), takes light of any retinal findings stating it is very rare if seen at all. However there is accumilating 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 (21), report that in their 3 cases presented none showed retinal involvement early, but definite albuminuric retinitis was found to develope in the late 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 urea excreting ability. This seems to be enough evidence to point out that given a case of true nephrosis that through the changes for retinal damage may be rare, ther should be a guarded prognosis until the patient is definitely on the road to recovery.

Albuminuric retinitis in pregnancy is know 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 causes. The occurance 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 developes early in gestation.

Uremic amblyopia 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 a 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 ~~dis~~ disease. It has been found in preparing this paper that there are many exceptions found 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.

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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 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 it's 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 comparitively fewer facts than in the others. This is by far the rarest 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. Albuminuric retinitis develeopes after the malignant hypertension results, and cardiac insufficiency with resultant edema is apt to defelope. 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 per cent 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 susceptable to intercurrant infection which is the common cause of death. It is true that pure cases may occasionally terminate in uremia .

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