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Prognosis of acute diffuse glomerulonephritis

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THE PROGNOSIS OF ACUTE DIFFUSE GLOMERULONEPHRITIS

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TABLE OF CONTENTS

INTRODUCTION.

In an attempt to clarify a problem which has long baffled me, I chose to write on a subject known as glomerulonephritis. This subject's importance and the volume of work written on it necessitated limiting this discussion to one phase of this process known as the initial phase or acute glomerulonephritis. There is truly a vast amount of literature concerned with this one phase alone and, therefore, this thesis will deal most pointedly with the outcome or prognosis of the acute phase. Of course the etiology, pathogenesis, pathological diagnosis, and treatment are indeed of great importance in determining prognosis but not so much of these subjects is presented in order to discuss more fully the main theme of prognosis.

One might gain a better idea as to the importance of glomerulonephritis by the remarks of P.C. Dietz (1). As a cause of death chronic glomerulonephritis is superceded only by heart disease, cancer and cerebral hemorrhage. "Every patient with an acute renal inflammation is a candidate for chronic and terminal nephritis and an evaluation of the extent of the lesion as a guide in the manner and continuation of treatment becomes apparent."

Much of the material to follow was gathered with the object of showing statistics over an extended period of

time after the disease has run its course; for only after a number of years can one determine what actually has been the outcome of the patient's initial infection. As will be pointed out in this material, too many physicians do not realize the far reaching and final possibilities of the early mild symptoms of acute nephritis.

The literature contained many references to studies made over a period of time on acute nephritis but each one had a slightly different criteria for following up the cases and, therefore, it is rather difficult to compare results of these authors. The correlation in most cases is close enough so that the numerous statistics give a fairly accurate idea of prognosis.

The following material will attempt to emphasize the necessity of recognizing this disease entity as such and following it until it is definitely known to be healed or what phase the lesion is in and what the patient may expect. It will be seen that there is nothing so new about the disease but that it is being recognized now more frequently and followed up in a methodical and careful manner.

In determining the prognosis we find that the more important problems are correct and early diagnosis. Also one must determine the stage and especially suspect the latent phase, proper follow-up and treatment. These

problems are the essential pitfalls which determine prognosis and each is a subject in itself and it is the hope that this thesis will clarify some of these problems.

HISTORICAL SURVEY.

The subject of glomerulonephritis cannot be adequately treated unless the early work of one of the more prominent men in this field, Dr. Richard Bright, is included. On October 12, 1825, Dr. Bright described a case which came into Guy's Hospital and by keen observation pointed out that the kidney was the organ at fault. The patient was suffering from edema, scanty urine and albuminuria, and autopsy showed small granular kidneys, enlarged heart and acute pericarditis. Of course this was a terminal phase of glomerulonephritis but it aroused enough interest in this disease that a great amount of work lead to our present conception of the phases of this process. (2). In 1836 he described a case of acute nephritis in his paper "Cases and Observations Illustrative of Renal Disease Accompanied with the Secretion of Albuminous Urine". This description leaves little to be said about the subject and the newer literature can actually add very little. The following is a description of acute nephritis by Dr. Bright nearly 110

years ago. "A child, or an adult, is affected with scarlatina, or some other acute disease; or had indulged in the intemperate use of ardent spirits for a series of months or years; he is exposed to some casual cause or habitual source of suppressed perspiration; he finds the secretion of his urine greatly increased; or he discovers that it is tinged with blood; or, without having made any such observation, he awakes in the morning with his face swollen, or his ankles puffy, or his hands oedematous. If he happens, in this condition, to fall under the care of a practioner who suspects the nature of his disease, it is found that already his urine contains a notable quantity of albumen; his pulse is full and hard; his skin dry; he often has headaches and sometimes a sense of weight or pain across the loins. Under treatment, more or less active, or sometimes without any treatment, the more obvious and distressing of these symptoms disappear; the swelling, whether casual or constant, is no longer observed; the urine ceases to evince any admixture of red particles; and according to the degree of importance which has been attached to these symptoms, they are gradually lost sight of, or are absolutely forgotten. Nevertheless, from time to time, the countenance becomes bloated; the skin is dry; headaches occur with unusual frequency; or the calls to

micturate disturb the night's repose. After a time, the healthy colour of the countenance fades; a sense of weakness or pain in the loins increases; headaches, often accompanied by vomiting, add greatly to the general want of comfort; and a sense of lassitude, of weariness, and of depression gradually steals over the bodily and mental frame. Again the assistance of medicine is sought. If the nature of the disease is suspected, the urine is carefully tested, and found in almost every trial to contain albumen, while the quantity of urea is gradually diminishing. If, in the attempt to give relief to the oppression of the system, blood is drawn, it is often buffed, or the serumen is milky and opaque; and nice analysis will frequently detect a great deficiency of albumen, and sometimes manifest indications of the presence of urea. If the disease is not suspected, the liver, the stomach, or the brain divide the care of the practioner, sometimes drawing him away entirely from the more important seat of the disease. The swelling increases and decreases; the mind grows cheerful, or is sad; the secretions of the kidney or the skin are augmented or diminished, sometimes in alternate ratio, sometimes without apparent relation. Again the patient is restored to tolerable health; again he enters on his active duties; or he is perhaps, less fortunate - the swelling increases, the urine becomes scanty, the powers of life seem

to yield, the lungs become oedematous, and, in a state of asphyxia or coma, he sinks into the grave; or a sudden effusion of serum into the glottis closes the passages of the air, and brings on a more sudden dissolution. Should he, however, have resumed the avocations of life, he is usually subject to constant recurrences of his symptoms; or again, almost dismissing the recollection of his ailment, he is suddenly seized with an acute attack of peritonitis, which, without any renewed warning, deprives him in 8 to 40 hours, of his life. Should he escape this danger likewise, other perils await him; his headaches have been observed to become more frequent; his stomach more deranged; his vision indistinct; his hearing depraved; he is suddenly seized with a convulsive fit and becomes blind. He struggles through the attack, but again and again it returns; and before a day or a week has elapsed, worn out by convulsions, or overwhelmed by coma, the painful history of his disease is closed." The latter part refers to some of the stages the acute phase may take, but complete recovery is not mentioned so at least something new has been added since a century ago. It might be added that he does explain that the duration of life after such an acute attack is an unanswered question because there has not been time or enough follow-ups to arrive at a conclusion.

Some of the earlier work in nephritis is written up in German and cannot be used here but Volhard and Fahr's classification and an elaboration of work by Lohlein on the fundamental unity of the nephritic process were great steps forward on the work in nephritis.

DEFINITION.

Cecil (3) defines nephritis and Bright's disease as "a number of diseases of unknown etiology, which may be acute or chronic and all of which are characterized by albuminuria and cylinduria and often by hematuria. In addition to these signs of local renal dysfunction which are dependent upon bilateral non-suppurative, inflammatory or degenerative kidney lesions, edema, hypertension and nitrogen retention are frequently present."

To Cecil's definition may be added that the acute diffuse phase is usually characterized by the sudden onset of hematuria, hypertension and edema and usually following an upper respiratory infection and especially scarlet fever or severe streptococcic infection. (4).

To more clearly illustrate a typical case of acute diffuse nephritis Moschowitz (5) is cited. It usually occurs in a young person and within 2 to 4 weeks after the onset of

a sore throat or scarlatina. The volume of urine is considerably diminished at the onset of nephritis to about 300 to 400 cc. or 4 to 5 cc per kilogram of body weight a day; it may even drop to complete anuria. Albumin appears in the urine along with hematuria and formed elements and oliguria. Puffiness in the face or extremities is soon noted, the blood pressure usually rises but rarely is the sytolic over 180 mm Hg. There is usually some increase in blood N.P.N. which is not very marked; headache is common. If high blood pressure persists and especially if the diastolic pressure rises, some degree of retinitis becomes manifest, as evidenced by hemorrhages and exudations in the retina with some tortuosity and irregularity of vessels and rarely a papillitis. Occasionally symptoms of uremia appear with marked cephalalgia, disorientation, twitchings and even convulsions. In the majority of instances, usually within a few weeks after the onset, clinical improvement begins. First the subjective signs disappear, the blood N.P.N. returns to normal, the hypertension and puffiness returns to normal, the hematuria disappears; the albumin persists longest even for weeks or months after all other evidences of nephritis have gone. Hematuria may persist in very small quantity over a period of several months and then finally

clear up.

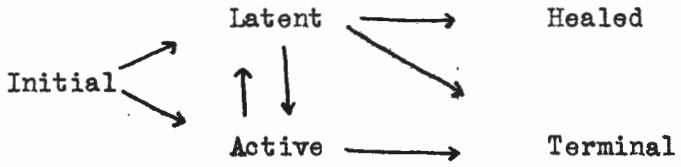
CLASSIFICATION.

The classification of nephritis has brought about many useless arguments which have served in no way to clarify this subject. Simmonds (6) put it quite aptly when he said, "it was evident that there can be no dogmatic, inflexible clinical or pathological classification of nephritis that will apply to any case of the disease throughout its entire course. The acceptance of this point of view should improve the treatment of the disease. With the understanding of the problems involved and a knowledge of the numerous variables and innumerable possible combinations of pathologic changes that can occur in the kidneys, the physician will treat the individual patient instead of the name of the disease."

A practical classification based on both clinical and tissue changes has been worked out by Volhard (7) and Jahr and Addès's equivalent follows it in parenthesis:

1. Glomerular nephritis (Hemorrhagic nephritis).
2. Nephrosclerosis (Arteriosclerotic Bright's disease).
3. Nephrosis (Degenerative Bright's disease).

Further breaking down the first division of glomerulonephritis which we are mainly interested in, Addis (8) sets up a chart which best describes what happens after the initial or acute infection.



The initial stage usually follows a streptococcic infection. Frequently this stage is missed but if severe enough the urine shows the red blood cells as a mahogany color. Red blood cells, pus cells and casts in the urine are pathognomonic. The casts may be made up of red blood cells. Usually there is a moderate increase in diastolic pressure and often a slight generalized edema. When the inflammatory reaction of the kidney has run its course, the renal lesion subsides in activity and if there is ultimate healing there is hypertrophy for compensation.

The latent stage may be due to a continuance of a focal streptococcal infection. Except for the urine, clinically the patient is entirely well and this may last for 10 years. The urine shows red blood cells and maybe a few red blood cell casts. During this period there is progressive glomerular destruction with hypertrophy.

The active stage may follow the initial phase of result from an exacerbation of the streptococcal infection in a patient in the latent phase. After some time a fatty degeneration may follow and it is accompanied by an increase in the number of casts and in the rate of excretion of protein and fatty hyaline casts. Red blood cells and casts may be the only distinguishing feature from nephrosis. With a disappearance of the infectious lesion the phase may heal or may go directly on after latent phase to the terminal phase.

The above description should partially clarify the meaning of the initial or acute stage, but there is still a further break down of the acute phase. Many fail to distinguish between acute diffuse glomerulonephritis and acute focal nephritis. Bennett (9) says focal nephritis arises during the course of an infectious disease as a complication. It is characterized by hematuria at the height of the infection. Edema and high blood pressure are absent and renal function is normal. Pathology is localized inflammatory lesions in the tubules and interstitial tissue. It is benign and subsides with the infection. Diffuse nephritis manifests itself from 2 to 4 weeks after the infection and every nephron is involved. The material here pertains to acute diffuse

glomerulonephritis. Longcope (10) has divided them into (a) those with a sudden onset and following or a sequel to any number of acute infections. These are the vast majority of the cases. (b)Those with an insidious onset and rarely preceded by an outspoken infection. In (a) there is usually a 3 to 28 day interval between the infection and the onset of acute nephritis.

MacAdam (11) makes the distinction between acute diffuse and acute focal nephritis. He says the latter has only slight malaise, pyrexia and edema and blood pressure is unaffected. It usually clears up after septic foci clears up and no permanent damage results. It is the prognosis of the diffuse type that we are dealing with.

To summarize this one might say that diagnosing all of the acute stages as one is a great mistake because we know that focal nephritis has a definitely far better prognosis than diffuse nephritis and one might also add that this may account for a variance in the observations on acute diffuse nephritis which have also included focal nephritis. Next we must not call a case of acute nephritis healed when it is progressing toward a chronic stage or especially when it is in the latent stage. Many cases of latent nephritis go undiagnosed and either go on to healing or later show up as a chronic nephritis when proper

care in the early stage may have lead to complete recovery.

ETIOLOGY AND PATHOGENESIS.

A great deal of experimental work in the field of production of acute nephritis in laboratory animals has been done with some success. Longcope (12) and Lukens found that both focal and acute glomerulitis could be produced in rabbits by injection of killed hemolytic streptococci infection. Longcope also says the immunological response between infection and onset of nephritis suggests the incubation period of serum disease. Thus a previous sensitization in experimental animals to hemolytic streptococci made them more susceptible to glomerulonephritis. Complete recovery from acute diffuse nephritis is rarely followed by a second attach. They can withstand serious streptococci infections. Smadel (13a) produced a diffuse glomerulonephritis by administration of the relatively organ specific antibody, so called nephrotoxin present in anti-kidney serum.

Many men now feel that the etiology of acute diffuse nephritis may be an allergic sensitization mechanism. The kidney reacts to the antigen in a specific and characteristic manner. The sensitization when restricted to one organ does not necessarily involve the entire vas-

cular tree of that organ; it may be restricted to particular parts. The spasm resulting from this allergic manifestation wherever it might be results in an insufficient oxygen supply. There may be an hereditary tendency to angiospasticity which would affect the progress of the nephritis. The time interval between previous infection and onset of acute diffuse nephritis is a strong point toward a theory of previous sensitization as in serum sickness.

The invading organism whose proteins are antigenic are usually cocci. The most common causes are scarlet fever, tonsillitis, pyoderma, otitis, sepsis, erysipelas, impetigo, pneumonia, influenza, and Volhard even included purpura. We now know that purpura follows the sensitization of nephritis. Scarlet fever has been over-emphasized and varying figures have given for its etiologic significance. Tonsillitis has its importance in that the incidence of this disease is so very high. Chilling as a factor produces a nephritis immediately which is different from the latent period in the other infections. Otitis is a fairly common etiologic factor and then ranking high are those cases with unknown origin (13b).

In most instances the acute stage occurs 2 to 4 weeks after an infection of the upper respiratory tract. Careful bacteriological examination has shown that the hemo-

lytic streptococcus (Lancefield Group A) is the organism at fault. Lyttle (14) and others in a study of 116 cases of acute glomerulonephritis following upper respiratory infections found a high anti streptolysin titer. Longcope (15) says the upper limit of anti streptolysin titer is 100 units and the lower level is 12.5 units.

Coburn and Pauli (16) set a median of 176 units and a natural level of 50 units. Lyttle, Laeb (17) and others found that with a primary hemolytic streptococcus infection and nephritis and a later hemolytic streptococcus infection, there were no clinical symptoms of nephritis. Denny (18) found that the progress of the nephritis after once initiated bore a direct relation to the persistence of the infection.

Seegal (19) studied the geographic distribution of scarlet fever, rheumatic fever and acute nephritis. She found a diminished incidence of the first two in southern climates but case incidence of acute nephritis does not vary with the latitudes studied. They are all supposedly a result of streptococcal infections and this might lead one to believe nephritis is not the result of streptococci infection but this has not proved to be the case.

PATHOLOGY AND HISTOPHYSIOLOGY

The nephron is the particular mechanism with which we are dealing and this is made up of the glomerulus and its tubule which in turn is made up of a convoluted and collecting tubule and the loop of Henle. This is a functional and structural unit. The capsular epithelium acting as a filter is probably one of the more important units and more emphasis should be placed on it, especially as a functional membrane. Its permeability is as delicately balanced as the works of a fine watch and even though there is no anatomical trace of interference, there easily could have been a functional disturbance. The kidney excretes nitrogenous waste products such as urea as they make their appearance, but it eliminates inorganic salts such as chloride and certain organic substances such as glucose only when the concentration rises above a threshold level. This mechanism insures a constant composition of the blood. This level may be regarded as a threshold, and the substances concerned may be called threshold bodies.

In the initial stage the kidney is usually enlarged and the capsule tense and stretched. It is a gray color and may be flecked with red dots which are hemorrhages into the capsule. Microscopically at first examination it may appear there is no alteration but upon closer

observation we see an inflammatory reaction within the walls of the glomerulus. In this early phase, the predominance of the inflammatory reaction is one of proliferation. There are three changes which may be followed through all the stages of glomerulonephritis. A proliferation of epithelium of the tuft, endothelium of capillaries and the formation of an intracapillary mass of hyaline fibers. All of these proliferative processes must eventually lead to a relatively avascular glomeruli. There also may be an exudate in the capsular space which may contain coagulated albumin, threads of fibrin, leukocytes and red blood cells. There is usually not much in the space because it is moved out into the tubules but this is not as important or constant as the intra capillary proliferation (20a).

It is important that the reversibility of the various processes be mentioned. That is the crucial point for the parting of the roads leading to complete healing, healing with defect or further and continued progress of the disorder. It is known that complete restitution occurs both clinically and anatomically. Arterial spasms, capillary paralysis and intracapillary exudate are probably reversible. Endocapillary proliferation may eventually lead to obliteration of loops and thrombosis of vas efferens, just as proliferation of the capsular endothelium

may cause the loss of a whole glomerulus. Necrotizing vascular processes preclude structural restitution. With the disappearance of intracapillary exudate by proteolytic enzymatic destruction blood re-enters the loop and there is an increase of hematuria which is a sign of improvement. Inflammatory reactions, depending on the defense powers, goes on at varying tempo. With the replacement of damaged tissues by connective tissue the kidney ceases to be the area of continuous unrest and the primary process becomes inactive but this is not always complete healing. The progressive tendency of the renal ailment depends upon the degree of loss of renal parenchyma and of vascular pathology. Lichtwitz feels that diminution of the parenchyma and of the renal circulatory bed below the point of a sufficient reserve automatically bring about progressive deterioration. (20b).

PROGNOSIS AND FACTORS INFLUENCING PROGNOSIS.

To begin, some remarks must be made about the variance in results of the numerous follow-ups of cases which this section presents. There are many things to take into consideration when discussing the prognosis of such an alternately progressive, recurring or latent disease.

From the literature I have gained the impression that too many men do not search hard enough or long enough to actually know what has been the actual outcome of an initial case of acute diffuse glomerulonephritis. Later I will go over the criteria for diagnosis and best methods of following the phases. At this point I will give a rare case of familial epidemic of acute diffuse nephritis to illustrate in a family the outcome of this acute reaction. Epidemic or even familial tendencies are very unusual in this disease, in fact this is the only case I encountered in the literature; but it so well typifies the course that I chose to start out with it. (21)

In a family of ten children ranging from 3 to 20 years of age, 6 came down with a mild sore throat, fever, coryza, headache and general malaise. This occurred during a period of 7 weeks. The initial case was in an 8 year old and it lasted 7 weeks. When the children did not respond to treatment at home in periods ranging from 1 to 6 weeks, they were taken to the hospital. The findings were edema in two of the children. On entrance to the hospital the urine showed albumin, red blood cells and casts. The 6 children were in the hospital from 6 weeks to a year and upon dismissal none showed abnormal urinary findings. Two and one-half years later, 4 of the children showed no

abnormal findings on urinalysis or physical examination. Two showed a slight trace of albumin and a few red blood cells. The phenolsulfopthalein test showed no renal damage and the N.P.N. was normal in these two children and they were believed to be in the latent stage. The interval between onset of infection and the nephritis was between 7 and 12 days.

This group of statistics has been collected from all of the available literature and although not all articles and figures were quoted, some of the conclusions have been derived from this large group of references. (22-40) From discrepancies found in groups of cases on statistics in glomerulonephritis, one author has advanced the following ideas as to the cause of these discrepancies: (1) there is great lack of agreement in cases; (2) failure of recognition of the latent stage of glomerulonephritis; (3) failure to make quantitative urinalysis of concentrated urine; (4) glomerulonephritis may differ geographically (41a).

One of the groups of figures quoted are from a recent article by Davis and Faber (41b) and was a follow-up on a number of cases by Snoke. It might be stated here that a variance in statistics given here may be due to the fact that some figures are for adults and some are for children. It is an accepted fact that the prognosis in children is far better than for adults. Aldrich's figures for 90%

complete recovery is the highest given but many pediatricians agree with this. Davis and Faber quote a figure of 81.3% complete recovery eliminating many variable factors and a close follow-up for over 2 years. These children were seen in the initial stage and these men felt that Snoke's same series gave a much lower incidence of recovery and higher incidence of mortality and chronicity, because many of the cases were not seen in the initial stage but in the later phases of glomerulonephritis. There was only an incidence of 7.8% of active cases after 2 years which certainly points to a bright picture in the outlook of nephritis in children.

After speaking with a pediatrician and following statistics of adults and children we see a great variance of opinions as to the outcome of the acute or initial phase. Many pediatricians feel that the incidence of chronicity and mortality is low enough that one might say that after getting the child safely through the initial phase in 4 to 6 weeks, the child may be allowed to go back to school or active life with protection to the extent of prophylactic sulfonamide protection or protection from hemolytic streptococci infections and watching for any recurrences. Aldrich (41c) says that in between 300 and 400 cases closely followed at the Children's Memorial Hospital there was almost 100% recovery. He also feels that there is not necessarily always an acute

attack of glomerulonephritis preceding a chronic glomerulonephritis. There are other pediatricians who feel the same way.

A striking example of a chronic glomerulonephritis without a preceding history of the acute phase was found at the University of Nebraska Hospital in 1944. A young boy 3 years old was admitted to the University of Nebraska Hospital with a generalized edema and ascites with oliguria, headache, nausea, and vomiting. There had been previous edema at the age of one and one-half years and a clinical picture of chronic glomerulonephritis was observed. There were recurrences and 3-week periods of hospitalization until the age of 3 when he had progressively become so bad. After death, 3 days after hospital entry, in 1944 the autopsy proved the diagnosis of chronic glomerulonephritis. There had also been red blood cells, casts and albumin upon urinalysis. The findings grossly were shrunken, waxy kidneys with pinpoint hemorrhages, narrowing of the cortex, poor kidney markings and mottled appearance. Microscopically there was a generalized picture of glomerular fibrosis and hyalinization, capsular thickening and some arteriolarsclerosis. The early appearance of chronic phase and lack of previous acute attack certainly raises questions in ones mind.

A comparison of Davis and Farr with other studies

shows a parallel with Lyttle and Rosenberg's early study with 79% recovery and 11% becoming chronic; Kahn, 85% complete recovery; Gachet, 90% recovery. Pittinos, Craig and Desanctis and Aldrich far excede these figures as they found almost complete recovery in all cases. Snoke and Cass show a far lower figure, below 60% recovery. These various opinions may be within statistical error but a figure of 80% complete recovery as a maximum is a figure quoted by many men.

The following are a group of statistics from a great number of articles. The methods of diagnosis were quite uniform but follow-ups and classification were somewhat varied, thus this does not give a complete table in all columns. Some classified under active were not only active cases but included the latent and maybe in some instances vice versa. Some fair idea of statistics on this subject though may be gained by studying the table. Most of the cases were followed on an average of from 4 to 5 years; some were over 10 years and a few as low as one year.

No. of cases	Time followed	Died %	Recovered %	Chronic %	Active %	Latent %
154	2 yrs	21.4	37		41.5	
170	$3\frac{1}{2}$-$15\frac{1}{2}$ yrs	12.6	41		43.5	
120	1-16 yrs		84.1	11.7	4.2	
114	13 yrs		90.5	6.1	3.4	
88	6 mos-5 yrs	3.4	64			32
		6	40	25		
		5	77	15		
150	2-14 yrs					
	under 30 yrs of age	11.5	49.5	39		
	over 30 yrs of age	24.5	49	26.5		
81	8.7 yrs average		80	20		
27	$1\frac{1}{2}$ - $3\frac{1}{2}$ yrs	7.4	66.6	15		11.3
29	1-7 yrs		41.4		44.8	13.8
56	$1\frac{1}{2}$ - 25 yrs		64.2		35.7	
102	over 2 yrs	10.8	81.3		7.8	

TABLE I

Finding the mean of each column may give a distorted view because it includes statistics for both children and adults. The figures for active and latent are probably not too accurate because some men included latent under their heading of active. There are variations from these figures

under certain set conditions and an average would be of less value than each author's own presentation of his series of cases. One of the men, Murphy (42) who has added much to recent literature should be quoted as a very good source for a numerical percentage on prognosis. The conditions presented by him give one a better idea of what the future holds for a patient who has had an attack of acute glomerulonephritis. Murphy says there is complete unanimity of opinion that chronic glomerulonephritis is the result of an attack of acute nephritis which failed to heal completely. Early diagnosis and good treatment serve in most cases to bring about complete healing. Acute nephritis is not such an innocent disease as was formerly believed. One may recover from an acute episode but this does not mean there has been complete recovery. His figures as originally given on 205 cases reported 10 years later seem to be a good guide although his incidence of chronic nephritis seems rather high and he may have included the latent stage in his classification of chronic. Fifty-one percent of his cases recovered, 36% became chronic and 13% died in that 10-year period. We do notice that he has watched them over a long enough period of time that his results should be quite accurate.

It will be noted in the table that he also gives some figures on 150 cases dividing them into two classes,

one over 30 years of age, and one under 30 years. There is a decided difference in his results in these two age groups. The rest of this article will attempt to deal with those things which influence the variations in the prognosis.

As, has been mentioned before, it is first of all necessary to recognize glomerulonephritis in the acute stage and, once recognized, proper treatment may be instituted and thus prognosis may be improved. Many recent articles have been written which have pointed out the necessity of recognizing the initial phase of nephritis and a criteria for diagnosis has been set forth. One author feels that the urine will show bloody urine, pus cells, some albumin, round kidney cells and very few casts. Clinically the patient will not appear to be very sick and there will usually be but slight edema. (43). The common consensus is that there is a sudden onset following some acute upper respiratory infection. The urine may or may not be grossly bloody and symptoms may be mild enough that without a good knowledge of the acute stage, one could easily miss the diagnosis. Casts made up of red blood are very significant upon microscopic examination of the urine. Albumin in the urine may be the first clue toward a diagnosis. The more inconstant signs as elevated blood pressure and variable edema must also be watched for. Thus one sees why diagnosis can be missed but a physician who is looking for a possible acute glomerulonephritis may

follow up his acute upper respiratory infections, expecially in the young individual, with urinalysis and in this way not miss the initial phase.

A great deal has been said about the significant signs and symptoms and laboratory findings in acute or initial glomerulonephritis which might be used as a guide to prognosis. The literature in the last 15 years has been in some disagreement as to what actually is of significance and what is not. Certainly no one man has had enough experience in his lifetime to ascertain the value of each test or sign or symptom. For that reason many authors' views are presented here. There are a few points which most men agree upon but where there is very much varied opinion one can be sure that the exact truth is not known.

Generally, it is said that 60% of patients with acute nephritis who recover will almost invariably do so within 4 months of the onset. Oliguria, hematuria and albuminuria may clear up within 7 to 10 days but there may be a delay up to 6 months. It is believed that the probable outcome of the acute attack cannot be determined during the first 10 to 14 days, but the best determination might be made after 6 months of close observation. Prolongation of the acute symptoms past 4 months leads with few exceptions to a permanent and ultimately fatal lesion. The amount of general disturbance in the early stages is far from a safe

guide to prognosis. In many cases there is found a tendency to dismiss the patient when the early symptoms have disappeared. Just as in rheumatic fever, this is a very fatal mistake and it is truly the time when closest observation is necessary. Addis' studies of the urine at this time may show renal irritation is still present and medical care is still badly needed. From this it might be assumed that it is very important to keep the patient in bed even though, early after the onset, the acute clinical symptoms have disappeared. To return a nephritic back to normal life at this time, where he will encounter fatigue, chilling and exposure to infections, will certainly tend to prolong the activity of his lesion beyond the four month period, and thus his chances of complete recovery will diminish. (44). Now we will discuss more specifically these guides to prognosis.

First of all proteinuria as a laboratory finding may necessitate a guarded prognosis whether arising from an acute nephritis or spontaneous in a previously healthy individual. (45). Murphy, (46) who has been quoted before, feels that if 10 to 25 gms. of albumin are found in the urine, it points toward increased activity of the glomerulonephritis. On the other hand, if there is a decrease in albuminuria it indicates that the kidney lesion is healing. Others feel that if the blood plasma albumin content becomes very low the majority of the cases will eventually become chronic.

Cases have been reported, in contradistinction to the above statement, in which proteinuria and low plasma proteins were as severe as in nephrosis, yet some of the cases went on to complete recovery. Edema influences prognosis only as it influences the immediate situation. If a patient becomes free from edema with hematuria on a salt-free diet, the prognosis is bad because only chronic nonspecific nephritis shows diuresis after a salt-free diet. (47). If proteinuria decreases early it may be good or bad but the longer it persists the greater is the chance of it becoming chronic. Thus it may be seen that the persistence of albumin after 6 months means a greater chance of developing into a later chronic phase but at the same time early disappearance of albumin does not necessarily mean a complete recovery.

Blood pressure, although it is a variable sign, has some significance in determining the outcome of the acute stage. There is usually only a moderate increase and it parallels other signs. A persistent high blood pressure, especially with a proteinuria, indicates probable chronicity. A rising blood pressure, even if the other findings are more favorable, is a very ominous prognostic sign. If the blood pressure has been elevated and gradually declines to normal, it is usually evidence of a healing lesion. There is a theory that a steady rise in the blood pressure

leads to increased intracranial pressure and its consequences. Some men do not believe that the degree of increase in blood pressure is of value but one can see that a persistent or rising pressure forebodes no good. (48,49).

There has been evidence presented that younger individuals have a better rate of recovery than older individuals, especially after the age of 30 years. It must always be remembered that the severity of the initial attack in general is never any indication of the outcome. The same may be said for the amount of hematuria; no definite prognosis can be made from the extent of hematuria nor its duration.

In a series of cases of 20 patients in which the foci of infection was not removed, Guild (50) found that only one suffered a recurrence of nephritis with another acute infection. Once a person has recovered from acute glomerulonephritis, he need not fear other infections. It has been found in many instances that these cases withstand secondary infections as well as a healthy individual. The type of infection preceding the onset of nephritis bears no weight as to what the outcome of the patient might be, and, as has been said before, the severity or mildness of the acute attack is no criteria for basing prognosis. Some workers have found that recurrent attacks which go to complete recovery do not adversely affect the ultimate

prognosis. One subject which has received much attention but in which varied conclusions have been reached, is in connection with the amenability of the infection or foci of infection to proper treatment. It has been suggested that much of the progress of the disease depends on the persistence of a foci of infection and that many cases will go on to complete recovery as soon as this foci has been removed. Cass found that removal of foci did not affect prognosis, severity of the initial attack, nor length of time in bed. Other inconclusive findings which cannot be a guide to prognosis are the number or types of casts in the acute stage, although red blood cell casts are supposed to be foreboding of a progressive lesion.

There are a few cases, approximately 5 to 12%, that die in the acute stage and they may show early signs or symptoms of uremia. In many of these cases there is increased edema, vomiting and convulsions. Death can occur within a few days to weeks, and may be due to renal failure, cardiac failure, or secondary inflammation. These might be considered complications of nephritis, meaning, of course, the latter two. Opühls (51) feels that the deaths in acute nephritis are not from the nephritis per se but that they are usually due to another infection added to the renal lesion. Another worker in this field has also added hypertensive encephalopathy or eclamptic uremia. He feels that

the deaths in the acute stage from this complication are usually over-emphasized and actually, if a patient is carried through this stage, the ultimate prognosis is no worse than an individual having an uncomplicated nephritis. These workers have found that myocardial complications are more common and serious than any of the others. They found that only about 2 cases out of 60 died of renal failure while approximately 15 out of 60, or 25% of the cases, died from some myocardial complication. (52). In a study of 138 patients, Whitehill, Longcope and Williams (53) found that circulatory insufficiency often forms an integral part of acute diffuse glomerulonephritis. These men observed that early in the acute phase, or accompanying the onset of the disease, there were characteristic findings of this insufficiency. First of all they found a paroxysmal dysnea or orthopnea. The heart showed changes such as enlargement and alterations in sounds and impulses. Sometimes they observed increased venous pressure and also liver enlargement. At times there may also be an edema which may be cerebral, pulmonary or kidney in location, and this edema could easily affect the function of these vital organs. In the mild attacks of acute nephritis these symptoms are quite rare while the moderate cases frequently show these characteristic signs. The severe acute cases presented these findings in the majority of patients. In the 138

cases studied in young adults, these men found a 71% incidence of the findings mentioned above. Appearance of these complications is an ominous sign and frequently there is death soon. It was found in another series of cases that there was an entity known as pseudouremia which was associated with a cerebral edema and was sometimes mistaken for true uremia (54). In such cases the uremia might clear up and not effect prognosis. Some cases with increase of symptoms as convulsions, edema, and vomiting may go on to a chronic active phase which will eventually mean death. Aldrich claims that convulsive uremia doesn't cloud the prognosis, because once the acute symptoms are over, the patient may go on to recovery. In a series of cases by her, it was found that, once the patient had recovered from the uremia, they were well when observed later. This possibly could be the convulsive psuedouremia mentioned above. Here is evidence for the cause of the 12% deaths in the early phase, and one must remember this possibility when a patient comes to the physician with acute diffuse glomerulonephritis. One must also keep in mind the fact that there are acute exacerbations of the chronic form which must be differentiated from the original acute infection as the prognosis is always extremely different.

The results of complications many times are fatal to the acute nephritis and there is not the problem of future

outlook. To me, what is going to happen to the average uncomplicated case of acute nephritis presents the most difficult and important problem. Proteinuria and hematuria have already been discussed, but this is not the whole picture. First of all we find that much work has been done on nephritis and its outcome. Until the last few years, the routine urinalysis has been done but no concentrated specimens have been routinly used. We now know that this is a serious mistake because the concentration method of Addis has been known as far back as 1925. At that time he and other men, through a great number of studies, set up standards for concentrated urine specimens, and it was even known then that there were urine findings which were found by this method and missed on routine urinalysis. The significance of these findings was also known. The Addis count is good because it reveals irritation and departures from normal function. Thus in mild acute nephritis, irritation is indicated by the casts, protein and blood in the urine while the function is indicated by the power to concentrate the urine and to clear the blood of urea. In the chronic phase there is little irritation, but the function has been largely lost. The Addis sedimentation count has been invaluable and also one of the more trustworthy guides in prognosis in that it detects the stage the patient is in and also picks up mild acute and latent stages which in the routine urinalysis would have been missed. The Addis

count (55) is run in the following manner. No fluids are to be taken after 4 P.M. and then all urine voided between 8 P.M. and 8 A.M. is collected; 15 cc of this total specimen is centrifuged at high speed for 10 minutes; 14.5 cc of the supernatant fluid is pipetted off and one drop of the remaining .5 cc is placed on a blood counting chamber and the number of casts, the red blood cells and the white blood cells in one or more large squares are counted. The calculations are as follows: N = the number of cells or casts in 4 of the largest squares, the volume counted is .4 cu.mm. Thus a ratio is derived:- $N = \frac{N \times 12 \text{ hr. vol.} \times 1000}{0.4 \times 30}$

Later Addis (56) ran some studies on 79 medical students for standards or normals. This is the rate per 12-hour period for adults:-

	Average	Lowest	Highest
Casts	1,040	0	4,270
Red blood cells	65,750	0	425,000
White blood cells	322,500	32,400	1,835,000

Lyttle (57), using practically the same methods found some normals on 161 counts: -

The Upper Limit of Normal in 12 Hour Excretion for 4 to 12 Year-olds.

	Lyttle	Snoke
Protein	35 mgm.	28.5 mgm.
Casts	10,000	0 - 29,000
Red Blood Cells	200,000	0 - 800,000
Epithelial and White Blood Cells	600,000 (male) 1,000,000 (female)	———

Another set of normals on adults by Goldring and Wyckoff is:-

Protein	3 - 60 mgm.
Casts	0 - 4,270
Red Blood Cells	0 - 425,000

These figures agree very closely with Addis and can be used as standard normals. Thus, the importance of a concentrated urine specimen should be brought out because it is used as a criteria as to whether a patient has passed the acute stage or is lingering in the latent stage. If a patient shows values above the normal, he can be kept in bed if still in the acute stage, or watched closely if in the latent stage, and in this way chronic glomerulonephritis may be prevented.

Another invaluable guide as to the phase a patient may be in, and also an aid in predicting the outcome of a patient who has suffered an acute nephritic attack, is the fluid intake and output, and the urea concentration test. The urine output should be two-thirds to three-fourths of the intake (58). Concentration tests may give the first indica-

tion of kidney damage. The tempo of renal functional impairment is the all important factor in determining the life expectancy of a patient with glomerulonephritis. No one test is a reliable index of the gravity of the disease, its course or prognosis, but results obtained from a combination of several measures performed at frequent intervals may be used as a fairly accurate guide. Van Slyke and others found that a normal urea clearance during the first months of the disease does not justify either a good or bad prognosis. It was found that a consistent rise of the urea clearance back to a normal within four months was essential for a good prognosis during the acute stage. Dietz explains the blood urea ratio:-

$$\frac{\text{Blood urea} \times 100}{\text{Blood NPN}}$$

as a very sensitive test of early renal damage. The average is 44% or less. The phenolsulfopthalein test detects functional disturbance of tubules and would not be of much value here. The concentration dilution test of Valhard is a simple but very effective kidney function test which requires the kidneys to concentrate under a strain, and is thus more revealing in the early phases of kidney function. One should allow 24 hours between the concentration and dilution tests. When the specific gravity is less than 1.029 for all of the concentration test there is impairment. In the dilution test, if only a small portion of the required 1200 to 1500 cc of water is secreted in 3 hours and only a

relatively high specific gravity of 1.010 or 1.012 is maintained we find some impairment. The normal kidney will excrete the entire 1200 to 1500 cc in 3 hours and will dilute to 1.002 to 1.005. It must also be remembered that the diluting ability persists longer than the concentrating power. (59). It has been observed that the reserve power of the kidney is temporarily decreased during the acute stage in all cases. If there is not complete recovery though, the concentration test will not come back to normal.

The blood urea clearance test in a series of cases showed that the renal function fell to as low as 10% of the normal in the acute stage but this was not inconsistent with complete recovery. In all cases which improved or recovered, the blood urea clearance began to rise in 4 months after the acute hemorrhagic onset. The urea clearance test consists of giving the patient 150 to 200 cc of water, one-half hour afterward have him empty his bladder and note the time of completion to the minute, then discard. At the end of 2 hours have patient empty the bladder completely, measuring urine and estimate its urea. When the coefficient rises above 0.09 impairment of the power of the kidney to excrete urea is inferred. This test is of more value in later stages but is quite accurate even in early stages. (60).

Others have observed that the sedimentation rate shows a correlation with the Addis count. The Addis count

becomes normal about 4 weeks after the sedimentation rate. Of greatest prognostic significance is a return of both to persistent normal levels for a period of several weeks. (61). In the preceding material I have listed some laboratory and clinical methods of determining the phase of the disease after an acute onset of hemorrhagic glomerulonephritis. Not only does this bring out the phase but also it is a guide in therapy and a basis for making a prognosis. Not one but many of these methods must be used, especially the Addis count, kidney function tests, albuminuria and blood pressure changes.

The field of therapy in acute glomerulonephritis is a vast and much debated subject and although its importance cannot be over-emphasized, little time can be devoted to it in this thesis. Only a few points which might effect prognosis will be touched upon here. Crumpler found that in 17 cases treated with various "sulfa" drugs, there were some rather significant findings. These cases were diagnosed previously (3 days to a month) as acute, hemorrhagic nephritis, Sulfanilamide or sulfathiazole was given from 4 days to 6 weeks and liquids were taken freely. Eight of the patients were followed 6 months to a year. They were found to be completely well in that time even though one did develop rheumatic fever later but showed no evidence of kidney damage after 6 weeks of "sulfa". (62). Other observers used sulfa-

nilamide in patients a few days after the acute onset of the nephritis and compared them with control groups. The results showed a 74.3% complete cure with sulfanilamide and only a 52% without it. There was also a marked decrease in deaths during the acute stage, and the number of progressive cases. Before the time of sulfanilamide, treatment consisted of rest, diet and removal of foci. (62).

Actually with the exception of the sulfonamide drugs there is very little prophylaxis against acute nephritis. Chilling should be avoided because of the circulatory reflex from skin to kidney. Prophylactic removal of foci is doubtful as nephritis is usually the result of sensitization in the beginning. The kidney will be spared most effectively by a diet, the end products of which can be eliminated extrarenally. The volume of the diet, especially water content, should not exceed the amount of urine produced in 24 hours. Thus, a strict initial limitation of diet and water intake may shorten the course and brighten the prognosis. Later the intake may be built up after an initial diuresis has been produced. No "kidney medicine" is of any avail. These therapeutic measures mentioned above may aid the underlying process somewhat, and in this way brighten the prognosis.

Actually there are few diseases where the relationship between the lack of early and proper management, and the remote consequences are so apt to be overlooked as in acute

Nephritis. Few conditions occur where the immediate response to early and energetic treatment appears to be so fruitless and yet it is so productive in preventing the remote ill effects of the disease. The treatment is usually inadequate, and most of all, the patient is allowed to get up too early. Of course, many cases go untreated because the classical picture is absent or the milder form eludes the diagnostician. Thus, we find that early diagnosis and good treatment serves in most cases to bring about complete healing of the acute inflammation.

COMMENT.

It will be noted, that as in many other diseased, case studies by different men are difficult to correlate because each has not used the same methods and criteria. Some mean value, statistically, insofar as prognosis of acute glomerulonephritis is concerned, is arrived at merely by observing a vast number of different studies and evaluating the methods and criteria used. If 60 to 70% complete recovery is the approximate figure in adults after an acute attack of nephritis, one feels that it is really not such a mild and unimportant disease. Of course, we must realize that those cases which go into the, so called, latent or even the degenerative stage may eventually go to complete recovery which would raise the above quoted figure.

On the other hand, in children, as high as 90%, or even higher, of complete recovery has been offered. Thus, we do know that acute diffuse glomerulonephritis in children below 12 years of age offers a very favorable prognosis. A 6 to 8-week follow-up and prophylactic measures, especially against hemolytic streptococci infections, may be all that is necessary in children because of the difficulty in keeping a child down, and the high rate of recovery.

The material offered has attempted to present ideas which may aid in recognizing and following up the cases of acute glomerulonephritis, and, thus, in some slight way influence the prognosis of such an important disease. One must remember that the mildness of the original disturbance and the short course, proved by superficial laboratory and clinical examination, permits many cases to slip by and later drift on into the almost certain death of chronic glomerulonephritis. If the medical profession can check or protect in the acute stage in ever increasing numbers, another step forward has been taken in pushing back an encroacher upon man's health and life span.

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