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Acute glomerular nephritis

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ACUTE GLOMERULAR NEPHRITIS

by

WILBUR KEITH BENNETT

SENIOR THESIS

UNIVERSITY of NEBRASKA

COLLEGE of MEDICINE

OMAHA

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INTRODUCTION

A discussion of the diseases of the kidney, where-
in a review of the general subject is undertaken, should
not fail to mention the work of the great clinician,
Richard Bright (1). Through his clinical studies and
autopsies, Bright was the first one who came to a reas-
oning conclusion that the many and varied forms of kid-
ney pathology represented three stages of one and the
same process.

The initial process caused a mottling and softening,
followed by enlargement and infiltration in the second
stage, and ending with hardening and contraction.

Several years of toil and observation preceded
Richard Bright's publication in 1827. Many cases of
dropsical effusion were studied by him, both clinically,
and pathologically on the autopsy table. Through this
study he was successful in separating those cases caused
by heart disease and cirrhosis of the liver from those
cases caused by kidney conditions. Finally he was able
to draw a clear relationship between albuminuria, edema,
and renal disease. This in turn led to an attempt, by
him, to correlate all types of kidney disease with symp-
toms produced thereby. This he was not able to do,

and although we have progressed in the knowledge of this disease we can not correlate the symptoms with the stages of the disease after the initial stage has subsided.

In arriving at his conclusions, Bright found that some cases of anasarca which came to autopsy could not be explained upon the basis of heart, lung, or liver disease. Peculiarly enough in these cases, the kidney was the only organ showing any morbid changes. It was then that he started studying the urine in similar, living cases. Subsequently he was able to form a definite and positive correlation between the urine that was bloody and coagulable and the morbid kidney. No attempt was made by him to prove the etiology, but he believed that it was probably due to some disease process affecting the kidney either directly or indirectly.

Blackall (2) also very early realized there were two types of anasarca. One type, in which the urine was not coagulable, was benefitted with heart stimulants and diuretics. The other variety, one cause of which he believed was scarlatina, had both blood and serum in the urine. This second variety showed visceral damage to the kidneys while the other viscera were singularly free from pathology.

Addis (3) believes that, in considering the whole problem of hepatitis, there are good reasons for the

avoidance of the term of "glomerular nephritis" which says at once too little and too much. He believes that the term "hemorrhagic Bright's Disease" at least commits us to no special doctrine, and that since this disease is still one of those interesting subjects of which we know so little, it is possible to go on talking about it almost interminably since there exists no exactness to destroy discussion. What he has said is true if you compare this disease to others which include typhoid fever or pneumonia, for in those diseases there are certain defined entities as to the clinical picture and the concurrent pathological findings.

This review, as set forth in the following pages, will not contain a classification of the nephritides for essentially only one phase of nephritis is to be specifically dealt with in this thesis. This phase is the earliest lesion which presumably always takes place first, which in many instances undergoes complete resolution, and whether masked by its paucity of symptoms or whether it is so very evident by its overwhelming symptoms, may or may not lead to the chronic stage. Therefore regardless of lesions suspected by the clinician, or found by the pathologist, the initial phase of nephritis shall be called "Acute Glomerular Nephritis".

The disagreement in classification, without doubt, comes from the studies made by the clinician on the living patient and the studies made by the pathologist on the dead body. While these studies should, in the final assembly, reach the same end, they never do, but they do tend to flow separately and endlessly on and never merge.

From the clinician's standpoint nephritis is a disease within a disease. For example a patient has an upper respiratory infection and after a variable length of time has blood in his urine, his face becomes swollen, and he develops a mild hypertension. It is true that hematuria is common to many diseases, but it is only in the first stage of nephritis or the exacerbation of the latent phase that red blood cells, epithelial cells, casts, and a sufficient concentration of hematin producing H ions combine to produce the coffee like urine. This condition of the urine does not have to be present grossly; the spontaneous and unstudied description of the patient may suffice to bring the condition to our attention.

Hypertension is found in many unrelated diseases, but it is probably only in acute glomerular nephritis that we find curves of systolic and diastolic pressure

which day by day so smoothly and rapidly descend toward normal levels.

Edema is in itself of no diagnostic value, but it is only in the initial stage of acute glomerular nephritis that we find the particular elastic, non-pitting fullness of the skin of the whole body.

Hence we see that the clinician's certainty of recognition is based on the unique combination of three signs, each one of which is in itself unique. He has ample justification for his convictions, and he requires no confirmation from other sources or discipline other than his own.

We find a different state when we discuss the viewpoint of the pathologist. It is only on rare occasions that the pathologist is confronted with clinician's acute glomerular nephritis cases. The basis for the clinician's certainty of recognition fades away, and finally even routine urine examinations return only doubtlessly abnormal results. The unfortunate clinician, as a rule, has to bring to the autopsy table just the type of patient in regard to whose diagnosis he feels most insecure. Just as Addis so clearly explains, the clinician brings to the autopsy table an equally unfortunate patient who died in the University Hospital Ward. To such a patient, who had always to work for a living, illness was a disaster, not an excuse, and he

had foregone any memories of minor interruptions to health which his social opposites cherish. His story upon admission was typical; he was always well and strong until at last he was forced to "give in" to a progressive weakness, an unexplained and symptomless vomiting, a sudden blurring of vision or an increasing dyspnea on exertion. In such cases the clinician is lost in the multiplicity of lesions arterial, cardiac, and renal. He tells the pathologist, when the patient died of cerebral hemorrhage, cerebral thrombosis, of cardiac failure or of uremia, that the patient was arteriosclerotic, that he had albumin in his urine, casts in his urine and low functional tests. His diagnosis? Arterio-sclerosis and nephritis; but he can not tell the pathologist if the sclerosis was caused by the nephritis or whether the patient was nephritic because he was arteriosclerotic.

Likewise, the clinician can ask the pathologist the same questions which must remain unanswered because there is nothing definite upon which to base clinical pathological cooperative findings. The clinician reaches his own independent certainty, and the pathologist must, in large part, draw his conclusions separately. As

mentioned before, when clinician and pathologist rarely meet over a patient in this initial stage there is a complete and happy agreement of opinion.

Histology conforms and makes more concrete the clinical certainty, and the clinician's data adds significance to the interpretation of the histological abnormalities. Beyond the initial stage uncertainty grows and any certainty of opinion that might have been is lost in obscurity--an end which has no observed or remembered beginning.

Happily, the clinician sometimes has patients in whom he recognizes and observes the beginning process and subsequently he is enabled to keep in touch with the patient until the renal lesions ~~has~~ come to its full development and has led to the patient's death in uremia, or has so entirely healed that quantitative sediment counts yield results which are well within the limits of normal. The big reason that this follow up study is so seldom possible is that to many patients the greater part of the course of acute hemorrhagic nephritis is not a disease at all. Of fifty one who started out with a known acute glomerular nephritis, in one series of Addis' cases, only six remained constantly in clinical view. More than one half disappeared never to return again;

the remainder came back, one by one, to die in uremia after a period during which they were perfectly well, as far as they knew or as far as the clinician could tell by the use of methods of inspection, palpation, percussion, and auscultation.

Generally speaking, there is no group of patients studied which can enable us to set up criteria for the duration of acute glomerular nephritis for it is so variable. The duration is usually short in those whose lesions heal and long in those who do not heal and who subsequently suffer a nephritic death with one or several complications attending. Addis believes that the greater per centage of cases that heal do so in the first year, and in general there is no healing after the disease has lasted five years.

How are we going to be able to detect those that heal or have healed from those who enter a latent stage and progress insidiously into chronicity? A mere glance at urinary sediment will not suffice to differentiate a case of acute glomerular nephritis from degenerative lesions as is now termed nephrosis, or from atrophic lesions which are the result of renal arteriosclerosis. There is no such quick and ready answer, and according to Addis, for the very excellent reason that there is no such thing as a purely inflammatory, degenerative,

or atrophic renal lesion. For such a discriminatory evaluation of a stage of the disease, there would have to be determinations of the rates of excretions of the formed elements in the urine.

Addis says that in theory qualitative methods must be altogether abandoned since everyone has protein, casts, and blood in his urine, and there is no qualitative difference (theoretically) between a patient dying of acute glomerular nephritis and any healthy individual dying. Therefore, Addis believes that quantitative sediment counts should be done. According to his work, categorically we may say that any one has nephritis who excretes more than 100 milligrams of protein and more than 5000 casts in a twelve hour urine. If we accept such an arbitrary numerical definition, and sediment counts are made on all patients who fall within it, the rates which are obtained tend to fall into three main groups. The acute initial phase would be characterized particularly by a great increase in the number of red blood cells. Such a classification would remain arbitrary and without meaning until it is here shown to have both a clinical and pathological significance. It should, then, be of clinical assistance in diagnosis and prognostic forecast. It should be of pathological assistance in the sense that the groups into which it separates

patients corresponds to the histological differences in the structure of the kidneys.

It is no more feasible and probably less reasonable for the clinician to accept the pathologist's classification than it is for the pathologist to accept the clinician's classification. Why? Doesn't the pathologist subject the kidney to elaborate inspection? Doesn't he actually view kidneys that come to autopsy in different stages of the disease complex? Doesn't he have permanent records, both written and specimens, by which he can reconstruct the histological stages of the disease process? Yes, but while his material is susceptible to the most detailed elaboration in space it has no time dimension, but it is restricted to the moment of death. Any extension in time must of necessity come from the clinician with whom he doesn't agree, or must be added through the memory of analogous lesions seen in an earlier stage of evolution. Finally, the variations in the pathological classifications of the renal lesion should be enough to prevent the clinician from regarding the pathologist as the arbiter of any final and absolute truth.

This thesis then shall deal with that phase of nephritis upon which clinician and pathologist agree. The acute glomerular nephritis is a stage in a disease

for which there is no specific treatment, no specific prognosis, and no end to complications. The exact etiology is not understood, yet it is the one phase of a devastating disease, in which early recognition and careful supportive treatment can be managed and aid given to gain that beloved goal of every clinician, the complete resolution of the disease process. Although general considerations will occupy a considerable portion of this paper, particular emphasis will be placed on therapy and prognosis.

ETIOLOGY

There is as yet no definite proof of the cause of nephritis, that is, acute glomerular nephritis, while it is generally agreed that its onset may follow any infectious process, the acute upper respiratory infectious diseases are considered to be the most important from a numerical point of view. A further subdivision which finds favor, both in the experimental field and the clinical field, is the role played by the streptococcus. Streptococcal infections of the throat and the upper respiratory tract hold the highest favor as an etiological agent.

Bright in 1827 and Blackall in 1825 both remarked that in many of their cases of nephritis the preceding or concurrent disease was scarlatina. In more recent years Löhlein (4) in 1907, Fahr (5) in 1912, Volhard and Fahr (6) in 1914 all came to the conclusion that by far the greater percentage of cases of acute glomerular nephritis was preceded by a streptococcus infection. In the collected cases of Volhard and Fahr 1914, one-fourth of all cases of acute glomerular nephritis that were associated with infections followed tonsillitis, and almost three-fourths or one-hundred-twenty-five of one-hundred-seventy-nine cases were associated with infections

of the upper respiratory tract.

Hill (7) in 1918; Bell and Hartnell (8) in 1920; Kozguski (9) 1919; Stolz (10) 1925; Fleckner (11) 1926 all obtained statistical data which leads to confirm the fact that streptococcus infections, especially tonsillitis, precede directly or accompany the onset of the greater percentage of cases of acute glomerular nephritis.

Longcope (12) 1927 did a conscientious piece of research wherein cultures were made from all obvious infections and it was found there was an actual incidence of streptococcal infection in 85 per cent of the cases. Cultures from infections in thirty two cases showed Beta hemolytic streptococci in 68.7 per cent and Alpha streptococci in 12.2 per cent. Ten cases constantly observed recovered from the acute nephritic attack and 90 per cent of these showed disappearance of the infection and infecting organism. Twelve cases constantly observed progressed to a chronic stage or terminated fatally. In ten of these or 83.3 per cent the infection or the infecting organism has persisted. No evidence pointed toward any proof of an actual streptococcic invasion of the kidney, for blood and urine cultures were all negative. Such evidence as this is indicative that preceding streptococcal invasion plays a large role in etiology, probably on a toxic basis, from toxins liber-

ated by the organisms. The exact mechanism for the production of acute glomerular nephritis was not indicated.

Winkenwerder, McCleod, and Baker (13) 1938 reported on a series of ninety-two cases. Following the methods of Longcope, cultures were made routinely from existing lesions. They found that preceding infections other than those of the upper respiratory tract were so rare that they scarcely mention them in their report. This is not to convey the idea that nephritis does not develop from other causes, but to enhance and emphasize that it so often follows the respiratory infection. Streptococci predominated bacteriologically and the tonsils and pharynx predominated organically. In the active stages, cultures were 80 to 90 per cent positive while in those patients who recovered from acute glomerular nephritis, organisms were no longer obtained in 68 percent. In the group with progressive nephritis, the incidence of positive cultures remained very high.

Murphy (14) believes that many doctors and more patients do not consider a mild attack of such respiratory diseases to be of any consequence, when in reality such an opinion is ridiculously wrong. This fallacious opinion is a hold over from the old belief that infectious diseases such as scarlet fever and septic sore throat

were the chief forerunners of acute nephritis.

Murphy's series of cases published in 1938 show that 66 per cent of his acute glomerular nephritis cases were associated with simple, uncomplicated upper respiratory infections. This 66 per cent of the entire series represents a total of ninety-nine cases. Winkenwerder and others found that 67 per cent of their cases were preceded by upper respiratory infections which occurred as tonsillitis in 44 per cent of the group represented as 67 per cent of the total. Volhard (15) has taken special care to emphasize the importance of the tonsillar ring and its diseases in connection with the etiology of acute nephritis. He believes that 75 per cent of all etiological causes are upper respiratory tract infections. Longcope (16) shares this belief.

Loeb, Lyttle, Siegal and Jost (17) worked on the prodromal infections causing acute nephritis on the basis that most cases are the result of an infection by the hemolytic streptococcus. This work was undertaken for two reasons:

(1) To contribute to the certainty of the etiological cause.

(2) To disprove that the myriad of diseases cited in the literature are seldom the forerunner of acute glomerular nephritis, a few of which are influenza,

diphtheria, measles, common cold, sore throat, simple exposure, osteomyelitis, pregnancy, intestinal catarrh, pyoderma and numerous dermatoses.

The research as undertaken was a very difficult task for nephritis seldom develops during the acute phase of the prodromal infectious process. The clinical and bacteriological evidence of the infectious process was often too far removed for direct bacteriological study. To get around this difficulty these workers decided to determine the antistreptolysin titer in individuals suffering from acute glomerular nephritis. Preceding their work in this field was that of Coburn (18) and Pauli who found that of one-hundred-forty-six normal individuals, 75 per cent has a titer of 100 units or less. Longcope (16) found that in 55 normal individuals the titer was between 25 and 50 units in 75 per cent.

Accepting this work as a basis or the normal value, Loeb et al arbitrarily decided that any titer over 125 was indicative of a recent streptococcus infection. One hundred-sixteen cases, consecutive and unselected and confirmed acute glomerular nephritis, were seen over a period of four years. Of these 104 cases had a definite prodromal clinical diagnoses as follows:

1.	Mastoiditis	29
2.	Cervical abscesses	15
3.	Sore throat	14
4.	Scarlet fever	11
5.	Cervical lymphadenitis	11
6.	Common cold	8
7.	Otitis media	8
8.	Pneumonia	3
9.	Peritonitis	2
10.	Measles	2
11.	Sinusitis	1

TABLE 1

Of the one hundred-sixteen patients twenty-five were adults and ninety-five were children. Males predominated 2:1. All patients were observed in the acute phase of glomerular nephritis, and they were followed through to complete healing or to development of the chronic process.

They found:

1. The maximum titer is usually reached in the first few weeks following the onset of the nephritis.

2. In 94 per cent the titer was above 125 units.
In 27 per cent the titer was 1000 to 2500 units.

3. In two patients with titers of one hundred-twenty-five and less it is significant that in two years and three years after, the titer was seventy-two units and seventy-one units respectively.

4. In a case of acute glomerular nephritis following lobar pneumonia type III there was no increase in the antistreptolysin titer; it remained between thirty five and sixty two during the acute phase and for fifteen months following.

A correlation was attempted between the maximum antistreptolysin titer and the degree of infection in one hundred-one patients. Peritonsillar abscess; cervical lymphadenitis which progressed to abscess formation and mastoiditis were looked upon as severe infections. The severity of the nephritis was gauged by the degree and duration of the urinary changes, hypertension, edema and nitrogenous retention. The summary of this correlation is as follows:

Infection vs. Nephritis

	Titer units						
	No.	:2000:	10-:	144-:	200-:	500-:	1000-:
		:2500:	125	:166	:333	:833	:1666:
1. Severe infections:	:	:	:	:	:	:	:
with mild nephritis:	51	:.3	: 1	: 2	: 11	: 11	: 22
2. Severe infections:	:	:	:	:	:	:	:
with severe nephritis:	12	: 0	: 0	: 1	: 3	: 4	: 4
3. Mild infection	:	:	:	:	:	:	:
with mild nephritis:	17	: 0	: 2	: 0	: 6	: 8	: 1
4. Mild infection	:	:	:	:	:	:	:
with severe nephritis:	21	: 0	: 2	: 1	: 9	: 7	: 2

TABLE 2

There was no correlation between maximum antistreptolysin titer and the rapidity with which healing occurred or the disease progressed to the chronic stage.

The development of maximum antistreptolysin titer is definitely related to the type and severity of the acute infection which precedes or accompanies the acute nephritis, but has no relation to the severity or duration of the nephritis. Ninety four per cent of one hundred-sixteen cases show specific immunological evidence of having had a recent hemolytic streptococcus infection.

A great volume of work has been done on reproducing acute glomerular nephritis by experimental means. No doubt much of this is significant but it is too voluminous and too far removed from the clinical view-point to be set forth in this paper.

The general practitioner's view-point as to the etiology is rather vague. Twenty seven different ones, who had been out of school from ten to twenty six years were asked their opinions on etiology and about as many different answers were received. Nine believed that scarlet fever was the only disease from which acute glomerular nephritis developed. Five believed tonsillitis was the only cause; ten believed the etiology was entirely unknown and two believed that any upper respiratory in-

fection could lead to the disease. Upon questioning, all agreed that they had read very little recent literature, nine did not do routine office urines and eleven did not remember or ever having a nephritic case in their practice.

In spite of the evidence presented in favor of a preceding streptococcal infection, there are some notable men who oppose the evidence. Addis is a good exponent of this school. He believes that in spite of the facts that statistics point to a preceding streptococcal invasion-even though it may have gone unnoticed, it is hard to believe or understand how some workers can declare a unitary origin such as is attained in tuberculosis or malaria. Organisms that are as diverse as are the hemolytic streptococci of scarlet fever, erysipelas and tonsillitis and the streptococcus viridans may all be associated with the origin of this disease and that, irrespective of which of these organisms is implicated, the disease may be the same in so far as identity can be judged by our present clinical and pathological criteria.

Addis further comments that not only is there this difference in bacteriological agents, but there is the uncertainty as to the significance of the delay which usually occurs between the onset of the symptoms of the

streptococcal infection and the first appearance of the hematuria, hypertension and edema of the initial stage.

We, today, could take exception to his views. Granted that we do not know the exact mechanism of the etiology. Granted that there is a variation from acute infection to the development of acute glomerular nephritis. Granted that many more do not, than do develop nephritis who have streptococcal infections. However it is true that throughout the medical world it was a known and accepted fact that the pneumococcus was the cause of pneumonia for many years before we knew that there were thirty odd types of the invaders. Carrying the argument further we can say that many people harbor virulent pneumococci who do not develop the disease; many people suffer from a cold or sore throat or prolonged chilling for days before they develop a pneumonia. Agreeing with Addis in so far that we are yet unable to construct a formula for the etiology of acute glomerular nephritis, we disagree as to the probable etiology. The tremendous amount of clinical work in culturing organisms and determining antistreptolysin titers points assuredly to a streptococcal origin. Is the production of acute glomerular nephritis toxic? Anaphylactic? Arthus phenomenon? All these questions have been investigated clinically and experimentally. No conclusions

of the exact production or mechanism of production have been reached. It is yet an unknown quality and an unknown quantity both bacteriologically, anatomically, and physiologically. Therefore we shall consider no further the problem of etiology. Suppose we liken the disease and its etiology to a haunted house. Suppose we choose to believe in the presence of first one ghost, then another and another and then search for each. We find the slamming doors, the broken window panes, the creaky, uncertain floors, the evidence and signs of disintegration; the ghosts themselves we never see. Always the ethereal occupant in all its misty mysteriousness eludes our grasp, and although in our nervous expectancy we discharge our guns, the "little bullets" have as yet failed to reach their objective.

CLINICAL COURSE

In a discussion of the clinical course and the clinical picture of acute glomerulonephritis we must remember that both are extremely variable. Accepting the data presented under the etiological section, we expect nephritis to develop after a varying period of time following infection with the streptococcus hemolyticus. The patient usually complains of hematuria, puffiness of the face, headache, and a decrease in urinary output. If the disease is of the fulminating form, edema may become generalized, visual disturbances may occur, hypertension may become extreme, dyspnea marked, delirium, convulsions, coma, and death may ensue. These events may be accompanied by fever, anorexia, vomiting, anuria and varying degrees of nitrogen retention. The foregoing description represents a composite picture of all the more striking features of the disease, but as stated before the variances are numerable.

Clinically we seldom see such a classic picture. More frequently one or more symptoms or signs dominate the disease. The reflection from a mirror which reveals a bloated, non-pitting face may be the only symptom or objective sign. The mother noticing the dark reddish

rown urine and noting its scantiness may be the cause for attracting attention to the disease. Older people often complain of backache and weakness or pain in the loins. In others the disease may be so mild and transient that there are no subjective findings and objective findings are detected through routine laboratory work, if the patient happens to go to the doctor for some other cause. The diagnosis in these mild cases must be made by examination of the urine wherein is found the erythrocytes in the sediment. The patient seldom recognizes the symptoms of raised blood pressure. In fact the condition is usually mild, usually transient and may not even take place. In only about 10 per cent of the cases does the systolic pressure reach 180 to 200 mm. Hg. and the diastolic 110 mm. Hg. Closely allied with blood pressure changes are the cerebral manifestations with headache, nausea, and vomiting, somnolence or mental confusion arising therefrom. General clonic convulsions may ensue or convulsions may take the pattern of status epilepticus. Death is not uncommon following recurrent convulsive seizures. The cause is not uremia, but probably cerebral edema. These also occur in about 10 per cent. Eye grounds in acute glomerulonephritis are usually normal but papilledema, paling of retinal arteries and narrowing of retinal arteries

may occur along with the hypertension. Four cases with which we were closely associated showed quite extensive retinal hemorrhages and one case suffered retinal separation.

The heart frequently suffers for we must remember that an acute glomerulonephritis patient is suffering from a toxic condition before he gets the nephritis. There is a widespread capillaritis in the disease and no doubt the capillaries of the heart suffer in proportion to the general involvement. Some cases exhibit severe cardiac disturbances with dyspnea, orthopnea, tachycardia, pulmonary congestion with increased venous pressure, gallop rhythm, all associated with acute congestive failure. In such cardiac conditions, convulsions may precipitate death.

The urinary syndrome is also variable, but red blood cells must be present for a diagnosis. The volume of urine varies from complete anuria in 3 to 5 per cent to normal in other cases. The specific gravity is usually increased in keeping with a histologic picture of fewer glomeruli functioning and these glomeruli allowing less fluid to flow into normal functioning tubules. Albumin is also present in varying amounts and must be present for a diagnosis to be correct.

Thus we can readily see that the classical picture affords easy diagnosis, but the nephritic with minimal symptoms and findings presents the real problem. In the first place it is very difficult to convince him that he is sick, and in the second place he is just as apt to go into the latent and progressive form of the disease.

Longcope's (12) conclusions concerning the clinical course and healing of the disease were that if the infection is cleared up then the kidney pathology should clear up if no irreparable damage has been done. If, however, there are exacerbations of the acute infectious process then there is more apt to be recurrence of kidney manifestations with greater danger of the lesions progressing to chronicity.

Murphy, Grill, and Maxon (19) believe that many cases of nephritis escape detection for in the early stages of acute glomerular nephritis the symptoms may be so mild that they escape any notice from the patient or the less thorough practitioner. They believe that such patients are in the gravest danger of developing chronic nephritis for the reason that they take no care of themselves or receive care from anyone else.

Windenwerder, McCleod and Baker (13) carefully studied the prodromal period in a series of forty one

cases. As they reported, the prodromal period in scarlet fever was three to four weeks. In this series of forty one cases, in which acute infection preceded the onset of nephritis, adequate data was provided whereby the prodromal period could be determined.

1. As early as the third day in 3 cases.
2. As early as the seventh day in 11 cases.
3. As late as 28 days in 1 case.
4. An average of 10.9 days for all cases.
5. In 80 per cent, onset was in 7 to 10 days.

The greatest incidence of onset was during fall, winter and spring. The seasonal variations coincided with waves of infection of the upper respiratory tract occurring in Baltimore.

Infections arising during the convalescent stage do not necessarily prevent recovery, and after recovery has been established, do not cause relapses of acute glomerular nephritis. On the other hand, exacerbations are more frequently associated with streptococcic infections in the latent and progressive stages. This suggests that patients who are destined to recover from nephritis become refractory or immune to infections during the convalescent stage and remain so after recovery has occurred. In the latent and progressive stages this is not true, for then the patient seems to be more

sensitive to streptococcic infections. This would seem to be contradictory to Longcope's conclusions.

It is probable that recovery from nephritis depends largely on the capacity of the patient to react favorably to the infection. Disappearance of the streptococci infection in cases that go on to recovery and in cases which become latent, and persistence of the organism in the progressive stage of the disease might be manifestations of the presence or absence of resistance to infection. In most cases it appears that those patients who are reacting to an acute infection possess the capacity to react to hemolytic streptococci so that some form of resistance to the infection develops, and as a result recovery from nephritis follows and disappearance of the organism occurs. In patients with a chronic infection, this capacity to react to streptococcic infection is lacking, a resistant stage does not develop, and as a result the organism persists; the nephritis becomes chronic.

Loeb (17) believes that in the majority of cases the antistreptolysin titer begins to fall in the first or second month of the disease and in one half of the cases the titer is normal by the sixth month. In this period the nephritis begins to improve clinically as measured by the disappearance of hypertension and edema,

diminution in albuminuria and hematuria, and by the return of normal kidney function. This is in agreement with Addis and Winkenwerder.

Murphy and Rastetter (14) in a study of 150 cases concluded that although acute glomerular nephritis is usually diagnosed in textbooks by the clinical picture of hematuria, hypertension and edema, many of the milder cases will pass unrecognized unless special precautions are taken. This reference to the quantitative sediment tests, or special precautions, refers to Addis' work. The greatest danger, then, arises not from the nephritis but from a failure to recognize the mild cases from which there is just as much danger of the development of the chronic phase of the disease.

Bell (20) in his treatise on the pathology and pathogenesis of Clinical Acute Nephritis enables us to best visualize the components of the diseased organ and to best correlate the clinical and pathological pictures. Bell's (21) methods were unique. He sectioned the kidneys of patients who had acute nephritis but died from some other cause in the acute stage. He compared these with normal kidneys and with kidneys in various stages of nephritis. The basis for his conclusions may be stated:

1. In the normal kidneys the epithelial cells equal in number the endothelial cells.

2. In the inflamed kidney the endothelial cells of the glomerular capillaries exceed the number of epithelial cells of Bowman's capsule.

3. In the latent and chronic stages the endothelial plugged capillaries become fibrotic thus closing off the glomeruli with epithelial crests.

He emphasizes that there are innumerable transitional stages ranging from the mild subclinical to the extreme fulminating disease; all acute glomerulonephritis.

He emphasizes that mild subclinical forms may exist, pass undiagnosed and untreated and pass insidiously into chronic stage before it is realized that irreparable kidney pathology is present. This view is upheld by Addis, Murphy, Richter (30) and many others. His study included all cases of acute glomerulonephritis which exhibited impairment of renal function indicated by retention of nitrogenous products, decreased ability to excrete phenolsulphonphthalein, inability to concentrate urine, loss of large amounts of protein in the urine, bleeding from the parenchyma of the kidney and severe oliguria or anuria.

He concludes from his extensive studies that the hematuria is due to blood loss from minute ruptures of the glomerular capillaries. Bacterial toxins injure the capillaries weakening them thus making them unable to withstand the added pressure that is thrust upon their

walls due to increased local pressure. According to this study the erythrocytes that appear in the urine escape from ruptured glomerular capillaries, not from those plugged with endothelial cells and leukocytes through which blood cannot pass! These capillaries that are ruptured appear normal except for the minute tears and the fact that red blood cells can escape is evidence that no permanent damage is done.

The edema of acute glomerular nephritis is not well understood, but most investigators are inclined to believe that widespread glomerulitis is the picture plus increased blood pressure thus creating a dual coexisting condition of increased permeability and increased hydrostatic pressure. Loss of serum proteins cannot be accepted as the cause for in the initial stage of nephritis the proteins are not depleted to that extent.

Hypertension is probably due, according to Bell, to an increased resistance to blood flow through the kidneys. Bell and Pedersen (23) produced hypertension by obstructing one renal vein. Goldblatt (24) produced chronic hypertension by narrowing both renal arteries. From the literature surveyed the consensus of opinion is that hypertension is the result of increased resistance to blood flow through the kidney plus an actual anemia of the kidney due to the same resistance. Those cases

which fail to develop hypertension are not entirely explained but it is presumably due to a failure of the heart or the vasomotor system to respond to the stimulus from the diseased kidney.

Uremia or the degree of impaired function as measured by the non-protein nitrogen retention is not a valuable prognostic aid since the renal function may rapidly improve or deteriorate. Bell reiterates that impaired function is based on structural changes in the glomeruli. He finds that many of the glomerular capillaries cannot contribute blood for the formation of filtrate, hence if too many are so affected, anuria will result. In most of the damaged glomeruli there are usually at least a few open capillaries. The total glomerular filtrate is reduced in each affected unit, but the tubule of each unit is functioning and more units are operating at one time. Both the decrease of glomerular filtrate and the distribution of filtrate through a greater number of tubules where it is exposed to a greater reabsorptive surface tends to produce a concentrated urine. With increased tubular absorption it is probable that more urea passes back into the blood than is normal, as well as there being less glomerular filtrate. This opinion is partially concurred in by Dunn(25) and Fremont-Smith(26). Bell concludes that chronic nephritis

is a final transitional stage of acute nephritis, that the cause for prolongation of the vicious cycle of events is as yet unknown.

Murphy (31) believes that acute glomerulonephritis should be considered both histologically and clinically as a single disease entity. He, like Bell, believes that the clinical-pathological pictures vary, but these variations are expressions of grades of intensity of the disease. He believes that the clinical manifestations of acute nephritis may be few or numerous and can be conveniently classed in five chief syndromes:

Urinary; Edema; Hypertension; Retention of Nitrogenous products in the blood; Uremia, genuine or convulsive.

The following conclusions of Murphy will, in a measure, be repetition but for the reasons that it is the most recent work published and summarizes the opinions most concurred in they will be stated.

The main syndromes may all be present in a patient at the same time or they may be transitory or at times one or another of the syndromes may dominate the clinical picture for a period and then disappear to be replaced by another. The urinary syndrome is the most important because it is always present and easy to study; it varies the least; it is only means afforded us to diagnose the

mild case, In discussing the urinary syndrome Murphy states, in effect:

1. Oliguria may be the outstanding feature.
2. The output of urine may be fairly normal.
3. Specific gravity may be 1.025 or higher and the quantity of urine scant.
4. Specific gravity may be 1.018 to 1.025 with a greater volume--usually not true.
5. The whole gamut of microscopic evidence may be positive--redblood cells, white blood cells, hyalin casts, granular casts, and gross hematuria may be present.
6. Only microscopic hematuria may be present.
7. Albuminuria must be present for diagnosis.

Murphy concludes that in spite of these variants, and all or any should arouse a suspicion of nephritis, it is best to consider albuminuria as evidence of nephritis until it is proved otherwise. In his series the urinary syndrome was present in every case and occurred alone in 28 per cent. Since nephritis is not the only cause of albuminuria, the question arises as to whether we are dealing with febrile albuminuria or nephritis. We should believe always that nephritis is the cause until we can prove or disprove, as the case may be, by the presence or absence of albuminuria after the subsidence of the acute infection. The quantity of albuminuria is of little significance since it bears no relationship to the degree of glomerular damage. It is very doubtful

if the severity of the urinary syndrome bears any relation to conditions which appear later in life.

In fourteen per cent of Murphy's cases edema marked the onset. Edema in itself is a benign complication, for as in other disease processes producing edema, if the disease is eliminated the edema disappears without leaving any permanent damage. It serves a useful purpose as a diagnostic aid due to its peculiar distribution.

Hypertension in any nephritic is a serious omen, but it does not have to be present for unfavorable developments. Conversely hypertension may occur in the acute process and entirely disappear with healing.

Nitrogen retention and uremia occur about the fourth or fifth day of the disease and is probably caused by oliguria and anuria--a failure of the kidney to excrete its normal quota. If a case goes to diuresis and resolution the non-protein-nitrogen drops rapidly. If resolution does not occur, then we can expect the onset of the uremic syndrome.

Genuine uremia is the direct outcome of renal insufficiency. Convulsive uremia is not dependent on renal failure and non-protein-nitrogen blood level has nothing to do with it. High blood pressure associated with cerebral edema causes the convulsions. The eye-grounds show an albuminuria retinitis; the diastolic

blood pressure is usually 120 to 130 with narrowing of the optic discs, fresh retinal hemorrhages and fluffy white patches. Spinal fluid pressure varies from 150 mm water to 300 mm. of water. The convulsions are similar to epileptic attacks coming in the order of: convulsions; clonic convulsions; stupor; convulsive uremia is of less prognostic significance than genuine uremia, for genuine uremia means the kidneys have failed.

Peters (32) Believes in the same general considerations as Murphy. He believes that acute glomerulonephritis patients, who are under observation, follow a peculiarly uniform pattern as a general rule. The first signs and symptoms appear one to four weeks after the onset of a precipitating infection. If the onset is earlier, suspect antecedent renal disease. The ultimate gravity of the disease bears no relation to the severity of its initial phase. If the profession flatters itself that it has anything to offer the patient, the early recognition is a matter of utmost importance for two reasons:

1. Relatively favorable prognosis.
2. Apparent immunity conferred. The cured nephritis patient has no immunity to the infections which give rise to nephritis, but only to the type of response to which this name, nephritis, is attached.

McCann (38) also agrees with Murphy and Peters

concerning the various syndromes.

Hayman and Martin (29) in a study of 77 cases list the symptoms:

Hematuria	76
Albuminuria	75
Casts	61
Hypertension:	
Systolic 140 ↓	54
Diastolic 90 +	49
Edema	
Face	45
Legs	30
Pulmonary rales	18
Pleural effusion	7
Ascites	6
Nitrogen retention	33
Uremia	7
Convulsions	3
Vomiting	3

TREATMENT

In considering the treatment of acute glomerular nephritis, the literature of the last six years will be reviewed.

Day (33) states that since the work of Volhard and Fahr, modern workers have come to regard acute glomerulonephritis as the result of a local and general vascular reaction of an allergic nature. The general edema and the rise of blood pressure are referred to a widespread capillaritis with some vascular spasm, while the renal effects result from similar lesions in the glomeruli which are particularly susceptible because of their particular vascular arrangements.

Day found that many cases in Egypt present the picture of an acute glomerular nephritis with large numbers of bacilli in the urine. The case cited is one in which coliform bacilli were recovered and from which a vaccine was prepared. A dose of this vaccine (five millions) provoked a focal reaction marked by polyuria and a temporary increase in proteinuria. The blood pressure quickly fell to normal, the edema disappeared and proteinuria was reduced to a trace within a one week period. Further dosages had no effect.

The effective dose was quite small
The response was immediate.
Oral or intravenous administration was effective.

Because of these striking results further investigations were undertaken. The rapid action by mouth suggested that the active constituent, probably antigen, was readily dissolved and entered the circulation in solution. The prompt effect of small doses favored the idea that the process was a desensitization rather than an immunization. With the supposition that the kidneys might be excreting an antigenic substance in post-streptococcal cases, similar work was carried out in acute glomerular nephritis.

Bacterial antigens were adsorbed to a precipitate of protein; hence any serum globulin precipitate from the urine would contain the product sought for. The final product was slightly acid; it contained some suspended matter and a small proportion of urea.

The results of the treatment appear to be good. The series run is too small but the work appears to be worth following to find out if such a procedure could generally be applied to the disease. The mode of action appears to be identical as that in the bacillary nephritis. It therefore appears that the urine extract contains a substance of the nature of an antigen. The extract had no effect on normals, either on the renal

function or the blood pressure. Considerable doses of an autogenous urine vaccine were tried on a case of non-renal hypertension but there was no effect.

The results of this investigation support the theory that acute glomerular nephritis with edema and high blood pressure is of an allergic nature since it is favorably influenced by treatment aiming at desensitization and immunization. Since an allergic reaction depends on the exposure of a sensitized individual or tissue to the specific allergen, the effect of exposure to cold is probably that of bringing about some liberation of an antibody-antigen reaction that occurs when a neutralized mixture of diphtheriatoxin-antitoxin is exposed to low temperature. Day believes that under these circumstances freed allergen reacts with the sensitized glomerular capillaries, particularly during excretion when the concentration would be expectedly greatest.

This work of Day is the only one of its kind and we do not find it alluded to in the literature. It seems to us that there should be some work carried out on the subject to prove more conclusively that he is right or to disprove his work.

Kellett (34) believes that it is probable that in the majority of cases of acute glomerular nephritis the force of the reaction is spent within the first few

hours and that treatment must be limited to aiding tissues to recover from the damage they have sustained. It is, however, almost certain that if the working hypothesis (sensitization) is correct, it will ultimately be possible to recognize the onset of this type of response and prevent its occurrence by specific desensitization. Until then the treatment will have to be mainly symptomatic as it has been since the recognition of the disease.

Kellet states that however mild the attack, the following principles of treatment should be observed:

1. Put the patient to bed, comfortably.
2. Protect from external stimuli.
3. Avoid sudden changes in temperature.
4. Daily tepid baths.
5. No diuretics.
6. Starve the first three days.
7. Reduce fluid intake to a minimum for five days. One pint of lemonade each day is suggested.
8. Fluid intake governed by urinary output after the first five days.
9. The diet should be gradually increased to normal with proteins restricted to 50 or 60 gm. per day.

Kellet is of the opinion that the patient should be kept in bed until the urine is free from albumin and formed elements, and at the end of two months he be

allowed to gradually resume his former activities. He does not believe that the removal of foci will help the nephritic process since the patient is suffering from an over-response to an infection, and that more likely prophylactic treatment will resolve itself into detection of the individuals who are apt to over-respond. To treat such people would be to desensitize them, but no such therapy is at present available. With our present modes of treatment, he believes that we should remove foci of infection for protection against the possible development of nephritis.

Goodwin (35) believes that since the disease under discussion is preceded by acute infection elsewhere in the body; the treatment naturally begins with the treatment or elimination of this infection. When there is a localized lesion, such as a cervical abscess or otitis media, surgical treatment should be instituted. He believes that the presence of kidney damage is a positive indication for the radical surgical treatment of active foci of infection. He believes that sera is efficacious for patients suffering from scarlet fever or erysipelas. Sulfanilamide shows some promise in hemolytic streptococci infections. Good nursing care is of the most importance. The prognosis is favorable when the condition is uncomplicated. The vast majority of patients recover

quickly, completely, and without sequelae. This happens under therapeutic regimes that vary tremendously.

Goodwin lays down the following rules for therapy:

1. Restrict NaCl.
2. Rest in bed as long as there is hematuria and proteinuria.
3. If nausea is present the first few days, do not force food.
4. Magnesium sulfate 5 to 25 gm. every four hours to cause loose watery stools.
5. Magnesium sulfate, 25 per cent solution intramuscularly, in doses of 0.1 gm per Kgm. every four to six hours for cerebral edema.
6. Hypertonic glucose by vein every few hours for myocardial embarrassment.
7. Venesection may be employed for pulmonary edema.
8. Diet: The quantity of protein has little if any effect on the course of the disease.

Lyttle, (7) in 1938, studied a group of one hundred forty-four cases of acute glomerular nephritis. He believes, as does Volhard, that the treatment should prevent the different dangers which threaten during the acute stage and also should prevent irreparable damage to the kidney. He does not believe that transition to the chronic can be prevented but that death from the complications can often be prevented.

In forty of sixty-eight deaths, the fatality was due to cerebral edema, cardiac failure, uremia, renal

failure; twenty-eight deaths were due to the precipitating infection. From his clinical experience, Lyttle is lead to believe that in any death from acute nephritis all four conditions are present to some extent.

Whenever hypertension is present in a child with nephritis there are present three real threats to the life of the child; the brain, the kidney, the heart. Cerebral edema is treated with 4 to 8 cc. of 25 per cent magnesium sulfate solution given intramuscularly. The dose is repeated if the blood pressure has not fallen within two hours or if the blood pressure at a later period has begun to rise. With the intramuscular injection, 1 to 2 ounces of a 50 per cent solution of the same drug is given orally every four hours until the blood pressure falls or catharsis results. If convulsions are present 1 per cent magnesium sulfate, 100 to 150 cc. may be given by vein. Overdosage is indicated by slow, irregular respiration; if this occurs 5 to 10 cc. of calcium chloride should be given by vein. Although the physiological action of magnesium sulfate is unknown, empirically it is known that the blood pressure is lowered, intracranial pressure is relieved, and urine volume is increased. When this plan is followed, water intake must be liberal and should range from 1000 to 1200 cc. daily. Caloric needs may be disregarded until clinical

improvement and the appetite improves when a regular diet may be given. Oliguria and anuria is at times difficult to manage, but usually all that is needed is a little patience.

Cardiac involvement certainly indicates complete bed rest, but if cardiac failure ensues then in addition to magnesium sulfate, fluid and food should be restricted, venesection, 50 per cent glucose intravenously, digitalis, and strophanthus may be used at the discretion of the clinician. Lyttle believes that chloral hydrate and morphine are the best sedatives.

The problem of infections consists of two parts. The first part is that of managing the infection during the acute stage. The second part is in getting rid of the active infected foci of infection. The active infection during the course of acute glomerular nephritis should be eradicated. In these circumstances, nephritis should be regarded as an indication for operation and not a contraindication. Early in the disease we can count on enough cardiac and renal reserve to carry the patient through the operation. Lyttle has never seen harmful effects follow operations performed during the acute stage. Blood transfusion and specific serum therapy may be used when they are indicated. There is good indication that that in the majority of cases the proper treatment of severe infections has a favorable effect on the course of the acute glomerular nephritis. It

cannot be said that such measures prevent the development of chronic nephritis. Sulfanilamide has been used for the acute infections but there is as yet no evidence to suggest that they will prevent nephritis.

As far as the focal infections are concerned, Lyttle believes that nephritis is an indication for tonsillectomy, and that in hospital practise all tonsils should be removed from nephritics, for he has never seen the bottom of a tonsil by looking only at its top. The time for performing the operation has arrived when the hypertension has subsided, and when the throat is no longer actively inflamed. This condition is usually reached in two to four months after the onset of the acute nephritis. In very severe cases of tonsillitis, operate at once in spite of the gravity of the nephritis.

Leavell (36) states that as it is true of many other diseases in medicine, the number of different therapeutic methods and regimes that have been advanced in the treatment of acute nephritis is adequate evidence that an entirely satisfactory one is not yet available.

The fact that the mortality rate during the acute attack is around 5 to 7 per cent in practically all the reported series suggests that the therapeutic measures in present use do not alter the outcome of the acute attack with the possible exception of the emergency

used in the treatment of pulmonary edema and convulsions. There are few studies that give any information regarding the possible effect of early treatment on the incidence of late sequelae.

Leavell considers the most important general features to be the duration of the bed rest, the amount of fluids, the diet, and the removal of foci. The actual length of time the patient should be kept in bed is a difficult problem when economic and personality factors have to be considered. In acute nephritis it is not only the acute phase that has to be considered but the whole life of the patient since 20 per cent are left with residual changes. Some patients do heal completely, but in those who do not there is nothing to do in the way of treatment. What treatment is undertaken must be done in the early phase. Radical rest regime, keeping the patient inactive until all signs of activity including the urine examinations, have entirely cleared up or definitely become chronic, should be adhered to.

As to fluid administration, Leavell thinks it is logical to give liquid about equal in amount to the urinary output during the period when output is diminished, as long as the specific gravity is high, plus 800 cc for insensible loss. If the specific gravity is low, urinary volume reduced, and a retention uremia seems to be developing, it is justifiable to attempt to increase the output by giving up to 2000 cc. of fluid per day to

an adult, even when edema is present. Of course this would not be advisable in cardiac embarrassment and lung edema.

Diet is not only a problem that is quantitative, but also qualitative for many of these patients refuse food. Farr and Snadel (37) in their studies on the effect of the diet on the course of nephrotoxic nephritis in rats showed conclusively that after the first month the course of this experimental nephritis was markedly and adversely affected by diets containing 18 per cent and 40 per cent protein, as compared to a diet containing only 5 per cent protein. Keutmann and McCann (38) could demonstrate no adverse effects in human beings with nephritis when they fed the calculated maintenance amount of protein. This we do know, or feel that we know, caloric intake is not of primary importance for a week or ten days. Leavell believes the kidney would rest more if protein were eliminated from the diet for a short time.

There is not rationale for this because:

1. Protein is necessary for body maintenance and if it is not furnished in the food intake, then it will be furnished from endogenous sources.
2. The excretory products will be the same.

Others recommend salt be eliminated from the diet since all the excess is eliminated via the kidneys.

Leavell believes that treatment of definitely infected foci should be considered. He does not recommend that such foci be removed during the acute attack of nephritis.

Acute glomerulonephritis is a self-limited disease, in the opinion of Lueth, et al, (39) and because of this the chief concern of the physician is to maintain water balance, provide adequate nutrition, and obtain skillful nursing care. Careful clinical observation is needed during the initial phases of the disease, so that the complications may be readily detected and effective therapeutic measures instituted.

The problem that has to be overcome is a clogging of the majority of the filtering units of the kidney by the products of inflammation. At this stage very little urine is manufactured, and what little is passed contains a great deal of albumin, casts, red blood cells and nitrogenous waste products. This reduced quantity of urine is not sufficient to rid the body of its waste that normally passes through the kidney. The waste products are retained in the blood stream. Lueth says that in the next few days capillary buds spring from the endothelial cells and soon form a fully developed glomerular unit. An outline of his treatment follows:

1. Nursing and dietetic.
2. Complete bed rest is imperative--patient is to

be put to bed as soon as nephritis is diagnosed.

3. Expend every effort to keep the patient from chilling.
4. Provide a warm well-ventilated room. Flannel bed clothing adds to the comfort of the patient.
5. Keep patient in bed until hematuria, proteinuria, or casts disappear from the urine. If proteinuria persists after two months, allow the patient to gradually resume some of his former activity in the third month. Fewer cases of chronic nephritis result when early complete bed rest is obtained.

6. The diet should be designed to assist natural reparative processes. In 1914 Volhard and Fahr concluded that rest and diet were most essential, so they advocated a thirst-hunger, bedrest regime in 1914. All food and fluid were withheld for a period of three to five days in an effort to completely rest the kidneys. Very little urine was formed and passed as the result of this management. This was more successful than the older methods of forcing large quantities of fluid. Although many endorsed this method, it soon became evident that there were two serious objections to the procedure. The patient continually loses water via breath, urine, skin, and bowels. In effect, this procedure added the danger of dehydration to that of nephritis. Secondly, the starvation plus the fever often produced a mild acidosis.

Volhard, (40) then modified this plan by first

emptying the bowels by a saline laxative. In children or those adults weakened by previous disease, he allowed either a little fresh fruit, a few crackers, sugar water, one to two cups of weak tea, by mouth, or hypertonic glucose intravenously for the first few days. All other patients were on a strict hunger-thirst regime until diuresis set in. This regime of Volhard's has been variously modified, but essentially the idea is carried through. In the main, most clinicians allow some fluids, some food, and some use of hypertonic glucose until some diuresis sets in.

Lueth believes the Karrel diet best satisfies the conditions of sufficient fluid to supply the losses through vapor, the skin and bowels and also furnishes enough caloric intake to guard against starvation acidosis. Milk in the amount of 250 cc. is given every four hours during the waking day from 8:00 A. M. to 8:00 P. M. for the first four to six days. The milk furnishes 1,000 cc. of fluid and 700 calories daily. This is also below basal requirements, but it is much more than that given by the fruit juice diet. There are objections to the diet containing 300 gm. of protein and 1.8 gm. of NaCl; but there have been no proven ill results from them. Lueth believes that the simplicity and easy availability of the Karrel diet far overcome

any theoretical objections.

The theory behind the old diets, that consisted almost entirely of carbohydrates, was that the end products of metabolism of such diets were mainly CO₂ and water and hence did not involve the kidneys. Paralleling that is the other old theory of urinary formation which left out the now known concentrating process carried on by the tubules. We now know that such diets cause the kidney to filter and reabsorb additional amounts of glucose and water, so the kidneys are really not spared. Sodium chloride, glucose and water are constantly being filtered through the glomeruli. In these starvation programs the work of the kidneys is increased by the greater required reabsorption. The Karrel diet eliminates the dangers of dehydration and acidosis.

Lueth agrees with Addis that high or low proteins are of little moment. Neither shows any effect on the hematuria or urea clearance.

According to Lueth, in acute glomerulonephritis diuresis spontaneously begins after three to seven days. When this diuresis sets in a dietary adjustment must be made. The Karrel diet is increased to include fruit juices, fruits cooked or fresh, cooked vegetables except rice, corn, green peas or lima beans; also included

are oatmeal, tapioca or arrowroot pudding, baked potato, butter, clear jelly, sugar, honey and cream. The caloric intake should be adjusted to meet the basal requirements of the patient. Fluid taken is governed by urinary output. If laxatives are needed, mineral oil or milk of magnesia are advisable, but mercurials, as calomel, are contraindicated. Diuretics are rarely needed. If spontaneous diuresis does not occur after five days, 1500 cc. of weak tea within $\frac{1}{2}$ to $\frac{3}{4}$ hour early in the morning may promote diuresis of an unprecedented degree, with decrease in edema and a lowering of blood pressure. Probably, adequate intake of fluid from the beginning of the disease would make this unnecessary.

About the third to the sixth week there is a decrease of blood NPN, urea nitrogen, and creatinine, so that a third dietary adjustment is necessary. Proteins may be pushed up to 60 gm. in the form of fish, fowl, egg, milk, and bread. Fluid is generally held to 1200-1500 cc. daily and salt restricted to 5 gm., all spices and condiments prohibited.

Lueth states that the precarious time for acute nephritis is about six weeks after the onset when the latent period is reached. He says that patients with mild, latent or subchronic nephritis are not well under-

stood, but if they were treated as sick people regardless of findings or symptoms, then a greater share of success would be evident. They should be put on a dietary regime and complete rest.

Prophylactic treatment is also necessary. Care of patients with upper respiratory infections should be taken with an eye open for possible nephritis developing. Removal of foci of infection is important. In those cases where tonsils, teeth, sinuses, or other foci are the source of hemolytic streptococci, their removal by operative procedures is an important part of treatment. His results with sulfonamides are negligible. These drugs were most effective where there were active acute infections.

Murphy and Pietraszewski (41) studied the effect of diet on acute nephritis. They took into consideration the urinary changes, the height of the blood pressure, estimation of the renal function, attention to the erythrocyte count and sedimentation rate as measuring sticks to determine whether healing was taking place or whether the process was going on to chronicity.

Sufficient alkaline- or acid-ash foods were included to change the pH of the urine either to the alkaline or to the acid side. High acid-ash diets were comparable

to the high protein diets of other investigators, and the basic-ash diets while not strictly of the low protein type were definitely limited in protein from animal sources. The quantity of protein was not the primary factor, but the acidity of the urine was the primary consideration. High acid-ash diets were obtained by increasing meats and limiting fruits and vegetables.

The old idea was that only milk was tolerated. The acidity of the urine was the basis upon which the older clinicians based their theory that alkalinity would promote healing. Those ideas concerning the deleterious effects of a high protein diet, high acid-ash diet, and high urine acidity caused a rigid restriction of diet in both acute and chronic nephritis. The apprehension over kidney condition was maintained at the expense of general nutrition. Soon it was learned that the harm done by neglect of the patient as a whole, outweighed the beneficial effects to the organ.

Murphy and Pietraszewski found that patients were not especially benefitted by either a basic-ash or acid-ash diet; that changes in the diet from acid to alkaline or from alkaline to acid revealed no differences in subjective complaints or objective findings; there was no evidence of delay in renal healing on the acid-ash

diet; no significant change in blood chemistry occurred; blood pressure was not affected; the sedimentation rate was not affected and patients were more satisfied and thrived better on the acid-ash than on the alkaline-ash diet.

Hayman lays down his principles of treatment in a truly simple manner:

1. Diuretics are no good; no drugs are indicated.
2. If water will not produce a diuresis, nothing else will.
3. Albuminuria is not a reason for prohibiting meat.
4. If edema is present and persists, restrict salt.
5. For prophylaxis, protect the patient and remove foci of infection.

Murphy (42) states that in the general management of the disease we must remember that we are dealing with a disease of the whole body plus a disease of the kidneys. At the time of onset of the nephritis, the body is in a state of debilitation as a result of the antecedent infection. He states the chief aims of treatment:

1. Treat the causal disease.
2. Resolution of the renal inflammation. Further exposure to cold and infection must be guarded against.
3. Diuresis must be promoted to prevent uremia.
4. Extra-renal complications must be properly managed. The important complications that we must treat are:

Heart failure.
Convulsions with edema.
General and local edema.
Hypertension.

Treatment of the causal disease should consist of absolute rest in bed, in a room well ventilated and at a temperature of 70 degrees. The patient must be warm, but must be comfortable. Sweating is not an aid to treatment, although it is still indulged in by some practitioners. Fluids are necessary in spite of the edema; the proper amount of food, rich in vitamins A, B, C, should be allowed. Iron tonics are valuable as has been proven by generations of workers. Murphy likes to give iron and ammonium citrate in capsule form gr. 10 t.i.d. The bowels should not be drastically purged but should be kept functioning with moderate doses of saline cathartics such as magnesium sulfate, sodium phosphate, or magnesium citrate.

As concerns the diet, if the patient does not tolerate food well by mouth then hydration and nutrition should be kept up with several hundred to 1000 cc. of ten per cent glucose intravenously. A glass of milk given three or four times each day, augmented with fruit juices and cereals as indicated, is usually well tolerated, by the patient. Murphy believes that milk is still

the best food for nephritics.

Some clinicians believe that fluids should be restricted to the urinary output of the day before while others believe that not over 500 to 800 cc. should be given in any one twenty four period. Aldrich (43) among others, feels that fluids should be forced. The more modern treatments are aimed at relieving a distressed organ. In view of this there is probably no rigid rule. Murphy advocates the restriction of fluids only if there is severe hypertension and an increasing intracranial pressure. Otherwise it is safe and proper to give up to 2000 cc. per day. If there is a rising NPN and an oliguria which is stationary then fluids should be forced in order to promote diuresis. The presence of edema is not the deciding factor, and fluids are given in spite of its presence. Edema has little bearing on the outcome of the case and when compared to hypertension, brain edema, and genuine uremia its significance pales.

The promotion of diuresis is one of the most important functions of the physician, for severe oliguria and anuria will be tolerated only for a short time. If diuresis can be established the signs and symptoms of nephritis subside rapidly. While strong diuretic

drugs are contraindicated, potassium citrate gr. XX t.i.d. given in liquor ammonium acetate has been found to be very good. Notwithstanding contraversial opinions, remarkable results follow the use of hot wet packs in those patients where diuresis is desired. Some say that the urine thus passed is of too low a concentration to be of any benefit. Murphy believes that the effect is one of counter irritation and in some inexplicable manner causes diuresis, comforts the patient and brings about a sense of well being. We should not pack the cardiac patient or the extremely weak individual. While this procedure is being carried out, watch the patient carefully and remove the packs if untoward signs develop. In those cases where anuria has persisted for three or four days and has resisted the simpler therapeutic measures, surgical decapsulation often produced remarkable results.

The edema of acute nephritis seldom requires treatment. The therapeutic measures already outlined suffice for nearly every case. If generalized anasarca develops, a salt free diet and limitation of fluids to 1200 cc. is sufficient. If the edema becomes agravating to the extent of embarassing respiration and heart action, mechanical removal of fluid from the chest cavity is a good procedure. In dire circumstances mild diuretics may be

resorted to. Theobromine and sodium salicylate in doses of ten grains t.i.d. for several days in succession is as good as we have. Other drugs such as caffeine sodium benzoate may be given intravenously, subcutaneously, or by mouth in doses of gr. 3 or 6 several times daily. Within recent years, large doses of alkalis have been advocated in the treatment. Osman (44) recommends potassium citrate, sodium citrate, potassium bicarbonate, and sodium bicarbonate in equal quantities. The dose is about 60 gr., t.i.d.

Hypertension may be absent, but when it is present it seems to reflect the degree of severity of the kidney inflammation better than the height of the blood pressure. When the blood pressure rises rapidly to as high as 220/180 one may assume that there is a serious kidney lesion, for when diuresis sets in the blood pressure seems to fall. Hypertension is probably the cause of the pronounced brain edema which results in severe headache and at times, convulsions. If the patient is in distress, mild sedatives may be used such as a capsule containing phenobarbital gr. 1 and theobromine gr. V. These capsules may be used several times a day. Chloral hydrate and sodium bromide gr. xxx may be dissolved in 200 cc. of water and given by rectum.

For convulsions, morphine is the best drug. It can be given in doses of gr. ss. for threatened convul-

sions, sodium amytal gr. v to vii may be given intravenously. If nothing else relieves then do a spinal puncture or give 200 to 400 cc. of 50 per cent glucose intravenously. Disregarding all theories, when convulsions set in there is hypertension and increased spinal fluid pressure.

PROGNOSIS

The study of the prognosis shall be a review of the literature of the last six years. The work of each group of clinicians shall be taken up separately.

Richter says that most studies on prognosis are made on juvenile cases, except those cases of war edema and war nephritis. The mortality during the acute stage of nephritis is regarded as being low in both groups but the prognosis, both the immediate and the late, is probably more favorable in the young.

Richter's (22) study is comprised of 160 cases of typical, acute nephritis so diagnosed at the Peter Bent Brigham hospital during the period of 1913 to 1934. The ultimate outcome of all but thirteen of the ninety individuals who survived their acute illness, was determined by follow up studies. The sixty cases that were rejected were thought to be acute exacerbations of a chronic nephritis. With the exception of one case, all individuals were hospitalized for an average period of six weeks during their acute attack.

Ten patients died during the acute process, but five of these were thought to be due to the causative infection or some other incidental factor. Of the five patients who died of acute nephritis, four were in their thirties and one was in the sixth decade of life. Three

died of uremia, one died of bronchopneumonia, and one died of erysipelas.

Edema was usually confined to puffiness about the face, and swelling of the ankles. There was no relationship between the degree of edema and the prognosis. The amount of total protein, albumin and globulin, was normal or but slightly lowered. The presence of hypertension was also unrelated to the outcome, although the general rule that a gradually rising or persisting hypertension is an unfavorable sign was generally borne out. Only one of the three patients dying of uremia had any hypertension at all and then only to a very minor degree. Neither the presence nor absence of gross hematuria, present in forty per cent of the cases, had any bearing on the prognosis. Albuminuria, present in one hundred per cent of cases, had no positive prognostic indications.

In the follow up studies, most of the patients returned to the renal clinic. The criteria for complete recovery from acute glomerular nephritis consisted of normal kidney function tests, negative urine examinations and normal blood pressure.

Of the seventy seven patients, whose conditions are known, sixty two or eighty and five-tenths per cent are now chronic nephritics. Richter, agreeing with Chris-

tian (45), believes that albuminuria is the most delicate indication for the presence of a nephritis. Hence the duration, not the degree, of albuminuria may prove an aid in prognosis. Of the sixty two cured cases, the urine became free of albumin within two months in fourteen, within six months in thirteen, within ten months in four, and within a year in nine cases. One case cleared of albumin in one and one-half years and two in two years. Two patients represent that acute nephritis may heal after the albuminuria has been present for two years.

Richter's significant findings are:

1. The immediate prognosis is good.
2. There is no essential difference in the death rate of children and adults.
3. When albuminuria has persisted for one year or longer, the chance in favor of the process becoming chronic are about six to one.
4. A patient was considered cured if there was no evidence of nephritis at the end of one year.
5. The validity of (4) is borne out by the fact that of the forty two cases considered cured at one year, only two were found to have chronic nephritis at a later date.

Snoke (46) says that the ordinary tests for kidney function will remain normal in the latent period of the disease and continue to give negative results until at least half of the kidney is destroyed. He says that

since Addis' work dealt primarily with adults, it seemed worthwhile for him to report the results in the large number of cases in childhood, studied by the same method as Addis.

1. Quantitative analysis of suitably concentrated urine was employed.
2. Studied by the quantitative method over considerable periods of time, most of the manifestations of nephritis in childhood which are commonly regarded as basically different forms of the disease are found actually to be different phases of acute glomerular nephritis.
3. Individual variations of the duration of the disease are enormous.

He believes that the prognosis depends on a number of factors: the stage of detection, the duration of the disease, the age of the child, the degree of hypertension, the nitrogen retention of the blood, sex since males predominate. The type of infection antecedent to the nephritis, the intensity of the initial stage and the number and severity of complications are also considered equally important from prognostic standpoint. His prognostic findings are:

Cases	Healed	Duration			Dead	Dead or con- dition active: over 2 yrs.
		under 2 yrs.	over 2 yrs	total		
104	44	25	27	51	8	35
		24%	26%	49%	8%	34%

Table III

Smoke believes that an eventual mortality of about forty percent can be expected with some confidence. However he agrees with Addis and Longcope that this probably not fair because of the number of mild cases that are never detected.

Longcope believes that in the vast majority of cases the initial stage ends in a completely asymptomatic, quiescent, or latent phase which may last for years. Complete recovery is rare when the latent stage has lasted for more than two years. He believes that the prognosis is much poorer in those patients in whom the initial phase has never been detected, for the primary attack goes on insidiously and chronic nephritis is much more apt to develop.

Of the one hundred sixteen cases studied by Longcope, 58 healed completely; the disease is considered to be quiescent in 33. Since many of these latent cases have been under observation for less than two years many will probably heal, hence between 55 and 65 per cent will totally recover. Fourteen have died; seven in the acute stage, five in the active stage and two in the chronic stage. Five of the seven dying in the acute stage succumbed to a complicating lobar pneumonia; one died of erysipelas, one died of acute sinusitis.

The disease has progressed to the chronic stage in only eight patients.

In the insidious or the idiopathic group, only one out of 25 has healed, 5 were in the quiescent stage, seven were in the chronic stage. Twelve have died. In some of these patients the progress of the disease has been quite rapid, onset to death being only two years. Longcope believes that the prophylactic use of the sulfonamide drugs will eventually serve to improve the prognosis.

Snoke's first prognostic series was from Stanford University. Two years later he went to Rochester New York to make a similar study. This second report was done to determine whether or not there might be a difference in the prognosis as to geographical location. Exactly the same methods were employed in the second investigation. One hundred forty six children from one to fifteen years of age were included. Observations were from one to nine years after the original diagnosis. His findings are tabulated below:

	Rochester		Stanford	
	#	%	#	%
Lesions healed	76	74.5	44	40
Lesions active	14	13.7	52	47.2
Patient died	12	11.8	14	12.8
Cases not followed	139	----	20	----

Table IV

The above table represents cases having a history of the acute initial phase.

Lesions healed	77	72.6	57	37
Lesions active	15	14.2	64	41.5
Patient died	14	13.2	33	21.5
Cases not followed	40	-- -	24	-- -
	<u>146</u>		<u>178</u>	

Table V

The second table represents all cases of glomerular nephritis.

It is seen that the cases had a more favorable prognosis in Rochester. Twenty six or 78.8 per cent of the thirty three Stanford deaths were from chronic nephritis and only four or 28.5 per cent of the fourteen Rochester deaths were from this cause. However, in the Rochester series the initial stage was more severe and more patients succumbed during that phase of the disease.

In Murphy's study of over two hundred cases he found that 51 per cent recovered completely, seventy three or 39 per cent went on to chronicity, and 13 per cent died. These cases were followed for a period of study ranging from two to seventeen years.

He believes that there is no sure way to determine whether the latent phase is developing into recovery or going on into chronicity. This transitional period

must become recognized so that we will watch more closely for permanent pathology. There is no one test that is a sure indication for a positive prognosis. An outline of Murphy's aids in prognosis consists of:

1. A complete urinary study must be done. Quantitative tests for albumin must be done on twenty four hour specimens. If the albumin is diminishing, it is a good prognostic sign.
2. An Addis count done repeatedly will show whether red blood cells, casts, and pus cells are stationary or diminishing, or increasing. Progressive impairment of concentration ability points toward a progressive unhealing lesion.
3. A raised blood pressure returning to normal is favorable.
4. Blood urea studies should be done every ten days. If the rise in urea clearance is constant until normal or near normal values are reached the prognosis is favorable. If it fails to rise or drops after a rise, the sign is ominous.
5. A progressive anemia for which no other cause can be found balances the prognosis toward the bad side.
6. A sedimentation rate that returns to normal is a very favorable sign.
7. The general appearance of the patient is worthy of clinical consideration. As Leavell states, when the patient is not progressing so well, it is a mystery to the patient why he fatigues so easily, why his food does not taste good, why he has no mental ambition, why he is cross and irritable.

The effect of treatment on prognosis, although we have no specific treatment, is beneficial enough that it is mandatory. It safeguards the patient against repeated attacks of upper respiratory infections, rests a

weakened body, provides a beneficial diet, restricts activity for a long enough period to insure healing.

In Hayman and Martin's series of seventy seven cases they found that 67.3 per cent of those followed for periods ranging from eight months to eight years, recovered.

Addis says that healing occurs in the first year in 75 per cent of those who recover, and that there is no record of healing after five years.

It has been generally accepted that once healed, acute nephritis does not recur. There is little in the literature to support this opinion. Loeb et al described ten patients who had been observed through an initial attack of acute nephritis, through a healed period, and through a subsequent infection with hemolytic streptococci without developing another bout of acute nephritis. Boyle et al reported two children with two attacks with complete recovery from both. Hayman and Martin have never seen a patient with two clear attacks of acute glomerular nephritis.

SUMMARY

After reviewing the subject of acute glomerular nephritis there are certain conclusions that stand out very clearly. In the history we learn that the recognition of the disease is comparatively recent. Richard Bright laid the first permanent cornerstone from which the many workers who have come after him have been able to build ever upward and forward. Peculiarly enough that astute gentleman described the disease with such clarity that no one has much improved upon it. True, we know more about the disease and the work of the normal kidney than he did, we know the parts affected, we know the dire circumstances that may attend the process, but to him go the honors of a great, complete, and clear understanding of a little known disease.

The following table is representative of the opinion concerning the etiology of the disease; and this table is a good index of the antecedent diseases. It is plainly seen that diseases associated with streptococci are the most numerous.

	Murphy	Rastetter	Leavell	Falkers & Falkers	Longcope	Richter	Seegal	Volhard	Lichtwitz (48)	Hayman	Martin	Total	Percentage
Number of cases	150	82	68	116	100	218	71	94	77	976			
Sore throat and tonsillitis	21	21	0	68	37	94	17	28	27	313	32.1		
Upper resp. tract	99	10	31	0	27	37	8	9	17	238	24.4		
Otitis media and sinusitis	0	4	0	21	2	17	0	0	12	56	5.7		
Scarlet fever	2	8	0	9	4	9	19	3	2	62	6.4		
Skin infections	0	5	0	0	0	0	0	19	3	40	4.1		
Pneumonia	0	0	0	0	5	15	6	4	9	39	4.0		
Rheumatic fever	1	0	0	4	1	7	2	0	2	17	1.7		
Miscellaneous Infection	21	17	6	1	9	22	17	5	3	101	10.3		
unknown	6	17	20	5	15	17	2	26	2	110	11.3		

Table VI

A summary of the outcome of the disease is presented in the following table:

	# of cases	Died of acute nephritis (%)	# of cases followed up	# of years followed	Cured, %	Latent, %	Chronic, %	Died of chronic nephritis
Murphy and Rastetter	150	12.8	127	2-14	58.3		41.7	
McPhee and Kaye (49)	90	5.5	48	4-7	85.4		14.6	
Richter	100	5.5	77	8-14	80.5		15.5	4.0
Longcope	141	7.5	134	1-14	42.5	32.0	11.2	14.2
Falkers	68	6.3	41	1-11	56.0		19.6	24.4
Leavell	82		26	1-10	77.0	19.2	3.8	
Hayman and Martin	77	7.9	52	1-10	67.3	17.3	9.6	5.8

Table VII

Although nephritis is not an exact disease, and it does have a wide range of variations, it still is as much of a disease entity as many of the conditions that the physician is called upon to treat. Therapy has as much to offer in this disease as it has in many of the others. Properly cared for, nephritis would be high in morbidity, but it would have a low mortality.

Prognosis in nephritis is not a clear cut study with clear cut results. Figures vary with different workers. The three interesting parts of the prognosis are: Healed. Latent. Chronic. This in itself is a problem for the average practitioner cannot tell or find out the difference between the healed and latent stages if the latter is asymptomatic and presents no gross findings. Hence the importance of prognostic tables assembled with the aid of state and fellowship financed investigations. At long last, prognosis is beginning to be stabilized through years of follow up observations on the same patients.

Let us end this review with the plea that such findings are forced upon the attention of the general practitioners of the land, so that this disease may receive enough attention that many individuals can live their normal span of life as useful citizens, who now

die at twenty to forty; and who even then live the last ten years of that span as semi-invalids.

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