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Diffuse glomerulonephritis

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INTRODUCTION

In this paper an attempt has been made to sum up what is known about diffuse glomerulonephritis. No consideration has been given to embolic glomerulonephritis. While some theoretrical considerations have been given an attempt has been made to hold to facts and present in clear-cut form what is known about the disease and its treatment.

Any attempt to cover all the literature on such a subject would be an undertaking of the first magnitude and has not been attempted in such a thesis. For this reason, for the most part, only the works of better known and recognized authorities were considered. An attempt has been made to develop what is known about the disease at the present time. For this reason the references are confined mostly to the works of recent writers on the subject.

The term nephritis is sometimes used rather loosely in the literature. However, in this paper when the term is used it is to be taken to mean diffuse glomerulonephritis unless otherwise specified. Writers also refer to this disease as hemorrhagic or parenchymatous nephritis. The subacute stage of the disease is also referred to as the nephrotic stage of nephritis.

The several types of nephritis all have some symptoms in common. In this paper an attempt has been made to establish the major points of symptomatic, physical and laboratory diagnosis

of diffuse glomerulonephritis. Little mention has been made of the fact that many of the symptoms of this form of the disease are common to other forms of nephritis.

A broad consideration of the subject has been attempted. The principle idea in this paper has been to develop the pathology, diagnosis and treatment. While no chapter has been written specifically on diagnosis, the means by which a diagnosis can be established, i. e., signs, symptoms, and laboratory findings, have been considered to the best of the authors ability.

The main and final object of developing this subject has been to give the writer an understanding of the disease and its treatment.

ETIOLOGY

Glomerulonephritis is a disease which stands in close relationship with infections of various kinds, and appears to be caused by the action of bacteria or their toxins. The majority of cases of acute glomerulonephritis follow an acute streptococcal tonsillitis, and occur most usually from one to three weeks after the throat infection. On the other hand, acute glomerulonephritis may occur in the course of a more or less chronic infective condition of the nasopharynx or skin. In children it occurs in conjunction with chronic tonsillitis, suppurative otitis media, or eczema and impetigo. The disease may manifest itself without any acute exacerbation of the infection being observed.(9)

In adults a greater variety of septic foci are commonly found in relation to the disease; for instance, alveolar abscess, maxillary sinusitis, and pelvic infections in women. A certain number of cases of bacterial infection of the urinary tract also develop a true glomerulonephritis which is often very resistant to treatment. Sepsis is also known to play an important part in the developmant of the chronic as well as the acute cases.(9)

In a study of the forms of infection observed at the onset of ninety-two cases of acute nephritis Winkewerder found the following: tonsillitis and pharyngitis-4I, sinusitis-I4, pharyngitis-8, bronchitis-6, pneumonia -6, scarlet fever-2, abscess-2 typhoid fever-I, erythema-I, subacute bacterial endocarditis-I, rheumatic fever-4, otitis media-I and latent syphilis-6. This author also

made the comment that the nephritis came generally three to four weeks after the acute phase of the infection had aubsided.(II) Greenwood has also presented forty-four cases as follows: tonsillitis- I7, otitis media- 4, scarlet fever- I, and "pharyngeal sepsis"- I. In the remaining 2I cases no acutely septic focus could be found, although in all cases there was some sign of chronic inflammation in the tonsillar crypts, which led him to think that the infecting organisms could possibly be housed there. It was interesting to note in thes series of cases that they occured mostly in children, only eight being over the age of twenty, and the age of greatest susceptibility was between ten and fifteen years. Here the onset of the disease usually occured ten days to three weeks after the acute infection, which was generally an acute tonsillitis.(7) Longcope in a review of thirty-four cases occuring in the Johns Hopkins Hospital found the acute infections preceeding these cases to be as follows: tonsillitis- I5, tonsillitis and bronchitis- 3, sinusitis- 7, bronchitis, broncho-pneumonia, otitis and adenoiditis- 4, scarlet fever- 4, and cystitis and pyelitis- I.(4) The results of all these studies seem to point to tonsillitis at the most frequent predisposing infection to acute glomerulonephritis.

The bacteriological cause of acute glomerulonephritis has also been a subject of considerable study. Longcope, in a series of thirty-four cases studied found the bacteriology of the preceeding infection to be: streptococcus hemolyticus B type- 22, streptococcus hemolyticus A type- 4, pneumococci- I, staphlococcus albus- I,

gonococci- I, cases with no predominating bacteria- 3, and cases in which no culture was taken- 2.(4) In an article published a year later Longcope reviewed forty-eight additional cases with regard to bacteriology of the acute infection preceeding the onset of acute and subacute glomerulonephritis. His results in this study were as follows: streptococcus hemolyticus B type- 31, streptococcus hemolyticus A type- 7, pneumococci- I, Pfeiffer's bacillus- I, and no cultures and no predominating bacteria- 8. In this series it was interesting to note that the infections preceeding the onset of the acute and subacute glomerulonephritis were similar to the findings of earlier studies. The following was true in this series: tonsillitis- 24, sinusitis- I3, scarlatina- 4, otitis media, bronchitis, and pneumonia- 4, and infection of wounds and lymph nodes- 3.(5) Bell also mentions septic sore throat as being occasionally followed by acute glomerulonephritis. In his series the majority of cases were preceeded by an infection in which the hemolytic streptococcus was the main causative organism. Leohlein, Volhard, Fahr, Aschoff and Ophulsall agree that streptocci are chiefly responsible for acute glomerulonephritis. Ophuls was of the opinion that B. influenzae and B. coli may occasionally produce this disease.(2)

In the case of chronic glomerulonephritis the subject of etiology is very vague. As Leiter points out most of the cases occur without apparent preceeding infection and the disease process gradually overcomes the individual. Several attempts were made to produce

chronis glomerulonephritis in experimental animals in Leiter's laboratory. Uranium nitrate, crotalus venom, administration of lead by mouth and diphtheria toxin were used. While kidney lesions were produced in the animals they were not like those of chronic glomerulonehpritis. Diphtheria toxin gave a lesion similar to that of acute nephritis. In an extensive review of the literature in addition to his own research work, he concluded that chronic glomerulonephritis as yet had not been produced in any experimental animal and also pointed out that it's etiology has not been satisfactorily explained in the human subject.(3)

It has not been determined whether the bodies of the bacteria or some diffusible toxin produces the glomerular injury. In favor of the toxin theory is the absence of bacteria in the glomeruli and the diffuse uniform character of the lesion. Most of the glomeruli are usually involved. A few of the earlier workers described bacteria in the glomeruli, but Ophuls has pointed out that more recent contributors by careful histological examination, have failed to find bacteria in the glomerular epithelium. Sections from ten of Bell's acute cases failed to reveal any bacteria in the endothelium. It was suggested that the bacteria undergo rapid lysis in the endothelium of the glomerulus and consequently are not seen.(2)

An allergic basis has been suggested for acute glomerulonephritis. One of the main reasons for suggesting this is the fact that nephritis generally prevails from a week to a month after the preceeding acute infection has subsided. Proponents of this theory claimed this was the amount of time needed for the body to develop

a sensitivity to the bacteria causing the infection. Under Christian's direction in Peter Bent Brigham Hospital, Boston skin tests were carried on by Derick and Fulton. These were run on individuals with nephritis, or those who had had an attacked of nephritis and on others who were free of the disease. Their results were very difficult to conclude anything from. The percentages of positive skin tests for streptococcus hemolyticus B type were as high among individuals free of nephritis as they were in individuals who had the disease. It was noteworthy that many individuals who either had or once had nephritis gave negative reactions.(8)

To try and further establish the etiology of acute glomerulonephritis Lukens and Longcope tried to produce the lesions of the disease by injecting the bacteria and toxins of streptococcus hemolyticus B type into the renal artery of rabbits. In their work fifty-two rabbits were used for the experiments. Twenty-three had been infected or sensitized to the bacteria and twenty-nine were normal. Of the entire group twenty-five, of forty-eight per cent, showed acute lesions in the left kidney, and since similar lesions could not be found in the right kidney, which served as a control, it was concluded that the changes in the left kidney were caused by the vaccine injected into the left renal artery. Of the normal animals eight out of the twenty-nine had the lesions of acute nephritis present in the kidney when they were killed five to eight days later. Of the sensitized animals seventeen of the twenty-three had the lesions of acute glomerulonephritis present in their kidneys when they were killed five to eight days after being injected with the bacteria.(6)

From this rather careful work it was concluded that both focal and diffuse glomerulonephritis had been produced in rabbits by the injection of suspensions of heat killed hemolytic streptococci directly into the left renal artery. Similar lesions in the glomeruli could not be obtained by the injection of suspensions of bismuth oxychloride into the left renal artery of normal rabbits. This acute glomerulonephritis occured in only about one-half of the rabbits employed for the experiments. It was observed much more frequently in rabbits in which an acute localized streptococcus infection had been produced by the intracutaneous injection of living hemolytic streptococci, than in normal rabbits. The occurence of acute glomerulonephritis was usually associated with a well marked skin reaction to the filtrates of hemolytic streptococci.(6)

Peters recently has brought out more clinical observations that seem to illuminate the etiology of acute glomerulonephritis. He has found that the formed elements in the urine increase in most patients with scarlet fever at approximately the time when nephritis usually appears. He also disputes the idea that nephritis is a remote sequel of scarlet fever. He states from his clinical experience it does not usually attack those patients who have an uncomplicated convalescence, but rather those who have septic complications from which streptococci can be recovered such as cervical adenitis, sinusitis, otitis media, bronchopneumonia, etc. A similar point of view has been expressed by Longcope.(10)

Further clinical work has been done in attempting to desensitize patients with acute nephritis to organisms possibly causing the disease. Organisms from foci of infection from which these patients were suffering were removed and cultured. An attempt was made to desensitize the patients to them. This was of little value, however, in so far as it affected the course of the disease.(I3)

A few deductions are drawn in closing. There appears to be some definite relationship between acute upper respiratory infection and the onset of acute glomerulonephritis. As to bacterial etiology it seems to be associated with acute infections produced by hemolytic streptococci. The suggestion that it is an allergic disease due to the body becoming sensitized to the organisms is by no means proved. One needs to keep an open mind in regard to this. The etiology of chronic glomerulonephritis is largely unknown. The disease has not been reproduced in experimental animals. Neither has any concrete evidence as to why certain cases will progress from acute to subacute to chronic glomerulonephritis been presented. Only theories have thus far been advanced.

PATHOLOGY

The renal lesion in glomerulonephritis has been defined as that sort of a lesion in which protein from the blood plasma passes through the kidney into the urine and it damages but does not at once altogether disintegrate the architecture of the kidney. The lesion is of such a nature that it can become a part of the life of the kidney, entering into all the intricacies of its structural and functional reactions.(2I)

For convenience of study glomerulonephritis is divided into three stages pathologically and clinically. It should be pointed out, however, that the involvement of the kidneys is a more or less continuous process from the beginning to the terminal stage. One stage gradually passes into another, if recovery fails to take place.(20)

In the first or acute stage the kidney is usually enlarged and the capsule tense. Petechial hemorrhages are frequently found in the cortex. In Bright's original case the kidneys are described as being of the darkest chocolate color, interspersed with a few white points, and a great number nearly black; and this, with a little tinge of red in parts, giving the appearance of a polished finely grained porphry or greenstone. Ophuls has called it the large variegated kidney, because its discoloration contrasts strongly with the extreme pallor of the amyloid kidneys (large white kidneys). (I9) These kidneys weigh more than the normal kidneys and cut sections often drip with blood.(20)

The earliest microscopic change noted in the first stage of glomerulonephritis, according to E. T. Bell, is a proliferation of the endothelium of the tuft.(24) MacCallum lately has sponsored the view that these cells are extra-capillary and arise from the connective tissue cells between the capillaries.(23) Bell in a more recent article has disputed this and presented microscopic evidence to show MacCallum's view to be erroneous.(24) As the proliferative process continues the central part of the tuft gradually becomes filled with these proliferating cells and hyaline material. At the same time there is a proliferation of the epithelium of the tuft, which produces a thickened epithelial wall. Because of the endothelial proliferation and hyaline changes within the capillaries of the tuft, the glomerulus becomes somewhat of an avascular structure. In addition to these proliferative changes the capillaries of the tuft generally contain numerous polymorphonuclear leucocytes. In the acute stage the vascular occlusion is confined, for the most part, to the central portion of the glomerulus and usually some circulation is maintained in the region next to the periphery. In this way the glomerulus is not rendered completely avascular.(22) (24)

A fairly clear idea of what has really happened can be found in Leone MacGregor's work in which studies of individual vascular loops were made. In this work the epithelial cells were believed to be the first to react. They were believed to increase markedly in size and multiply so that they filled in the spaces between the loops of the tuft. Later the edematous epithelium may degenerate and

be cast off into the capsular space. Closely following and paralleling this is a proliferation of the capillary endothelium of the vascular loops. Numerous mitoses were observed in these cells. They were observed to proliferate to a depth of two to three deep, so that the loop was seriously obstructed. This obstruction was further increased by a proliferation of hyaline material within the capillaries. MacGregor showed this to be present in the earliest stages of the disease. This eventually, if the process continues, leads to hyalinization of the glomerulus. These hyaline fibers are seen only in association with proliferation of the endothelial cells, and are possibly formed in some way from these cells. At the disease progresses the fibers become coarser and more numerous until they form a dense network enclosing the proliferated endothelium.(I7)

In addition to the intracapillary changes there may be an exudate in the capsular space, which may contain coagulated albumin, threads of fibrin, leucocytes and red blood cells. This exudate, however, is seldom very abundant. The red blood cells are seldom seen in any number. In the tubules at this time they are often seen in abundance. They are probably swept out by the flow of urine and tend to collect in the convoluted tubules where absorption is taking place. This exudate is thought to be a mere accessory phenomenon. The essential change in glomerulonephritis is within the capillaries.(20)

In acute glomerulonephritis, microscopic sections under low magnification show enlarged avascular or nearly avascular glomeruli which have an enormously increased number of nuclei. The diameter of the glomerulus is often increased as much as fifty per cent. Large sections of the kidney may show the process to be diffuse throughout or somewhat limited to certain glomeruli. The cases in which the kidney is affected diffusely usually run a fulminating course. The patient expires from uremia in the acute stage of the disease. Where the glomeruli are partially involved the cases usually recover or gradually proceed to the subacute and chronic stages.(I3)

In the acute stage of glomerulonephritis the tubules may show slight degenerative changes. This depends on the degree of glomerular and other capillary involvement with the consequent shutting off of the blood supply to the tubules. Such changes in the tubules, however, are by no means typical of this stage of the disease.(I3)

In subacute glomerulonephritis the kidneys are large, more or less opaque and variegated. Some of them are studded with minute hemorrhages, others are more pale. The external surfaces are smooth and the cortices are somewhat increased in thickness.(I9)

The processes which began in the first stage have became very marked in the second. The essential changes may be roughly classed as glomerular, tubular, and interstitial. In this stage the deviation of the kidney from normal is very marked and can be recognized at a glance.(I3)

In the glomeruli there is an advancement of the changes already observed in the first stage. They are enlarged to three or four times normal size and are bloodless. In the capillaries there are the proliferative and obstructive changes already described in reference to acute glomerulonephritis and they have become further advanced. In addition there is a gradual hyalinization beginning in one portion of the tuft and gradually spreading until the entire structure is converted into a hyaline mass. While this process is diffuse some glomeruli are still found in the early stages of involvement while destruction in others is far advanced.(20)

In the more severe cases capsular changes are seen. While the capsular space may contain red blood cells, desquamated epithelium and coagulated albumin, this is of little significance. Fibrin may be present in varying amount both in the capsular space and between the capillary loops of the tuft threads of fibrin may often be demonstrated by means of special stains. However, the striking feature is a proliferation of the capsular epithelium, particularly the parietal layer. As a result of this proliferation the epithelium becomes thrown into folds which fuse of become bound together by threads of fibrin. This cellular mass that is formed is frequently confined to one part of the space so that it comes to assume a crescent form and is known as an epithelial crescent. In the course of time the crescent becomes converted

into fibrous tissue and the fibrosed crescent and fibrosed glomerulus fuse to form one hyaline mass. This process is, however, more characteristic of the third stage of this disease than the second.(20)

The obliteration of the capsular space is a striking phenomenon. It renders any further function on the part of the nephron impossible. The epithelial crescent, however, may not be the cause of obliteration of the capsular space. As E. T. Bell points out the tuft may become adherant to the parietal epithelium at several points. In this way it is obliterated in much the same manner as in a pleurisy when two surfaces come together. The hyaline tuft may also appear to fuse with the capsule. This may be due to desquamation of the layers of epithelium, both parietal and visceral, producing many of these desquamated and degenerating cells in the capsular space. The two surfaces will then readily adhere.(13)

At this point it might be best to consider tubular and vascular changes together. In glomerulonephritis the glomerular capillaries are first injured and the arteriolar changes follow. The dependence of the arteriolar lesions on glomerular capillary obliteration also explains why they are confined to the arterioles of the kidney and are absent in other organs. It further accounts for the frequent absence or minimal degree of endarteritis obliterans in most old cases of glomerulonephritis. When the blood supply and function of the tubules is removed they tend to atrophy and disappear. (15) (16) As the blood supply is cut off the epithelial cells of the convoluted tubules show cloudy swelling, fatty degeneration, or

actual necrosis. Many of these injured cells are cast off to form epithelial casts. The edema and high fat content of the cells are responsible for the enlargement and pallor of the kidney. In addition to neutral fat other lipoid material such as cholesterol ester may be found. The most important thing this tubular degeneration probably shows is that all parts of the nephron live a common life. Injury to one part will be reflected on another.(20)

The interstitial tissue presents a puzzling feature in this second stage. Small areas of round cells may be seen in it. These are confined to the cortex and are found in those areas which show most degeneration. From a study of inflammation it is remembered that they could possibly have a function in removing debris. However, in inflammation we generally see polymorphonuclear leucocytes taking this function. Aschoff states that these cells are reparative and concerned with the formation of connective tissue. However, when it is all summed up, the fundamental nature and meaning of this round cell infiltration is not known.(20) (21)

In the third stage of chronic glomerulonephritis the kidneys show marked evidence of contraction which is either diffuse, in which the surface of the organ remains smooth, or irregular, producing a granular, or sometimes even coarsely nodular surface. The capsule is thickened and adherent. The color varies from dark red with numerous hemorrhages, to a pale putty color. Some kidneys are more or less cystic. The cortex is narrow and the markings on the cut surface are indistinct. The kidneys are small and both of them do not weigh over one-hundred to two-hundred

grams.(I9)

On microscopic examination we see a structure which hardly resembles a kidney. The dominant feature is complete destruction of the normal architecture, and its replacement by the substitute, fibrous tissue.(20)

This condition is merely the end result of the pathological changes which began in the first stage. Addis has termed this another organ, for it is completely changed from the normal kidney. A hyaline mass of fibrous tissue is all that is left of what was formerly the capsular space.(2I)

While there has been a large destruction of glomeruli, curiously enough in this same kidney many glomeruli are fairly well preserved. Around these glomeruli there may be areas of regeneration. Oliver and lund have made a very important study of the kidney in this stage of glomerulonephritis. By means of both micro-dissection of individual nephrons in macerated specimens, and wax reconstructions of nephrons from serial sections, they have shown that some nephrons are of normal size, some are extremely atrophic, and some are markedly hypertrophic.(14)

The glomerulus in the hypertrophied unit was found to be about sixty times the volume of the normal glomerulus. In this the same as in the atrophic unit a sclerotic but patent inter-lobular artery gave rise to a greatly thickened afferent vessel which entered the ruft and broke up into a few distorted capillaries. A very thin-walled efferent vessel led from the tuft and entered

the intertubular network. Well preserved, discrete red blood cells were seen throughout all these vessels, so that it was reasonable to suppose that the circulation through the glomerulus was intact. Ludwig's anastomosing branch was not present. Inspite of the size of this glomerulus the number of capillaries present was found to be considerably reduced. Much connective tissue proliferation was found to be present in the tuft so that while the glomerulus was greatly enlarged it was also relatively avascular.(I4)

In the hypertrophied unit the change was relatively simple as far as the tubular elements were concerned. It was found to consist solely in an increase in the size of the proximal convoluted tubule. The other elements of the tubular complex remained unaffected, and there were no significant alterations in the topographic relation of the various parts to each other. The proximal convoluted tubule as well as being increased in diameter was found to be increased in length also. The character of the epithelium was not entirely normal. Morphologically irregular cells were found.(I4)

In the atrophied unit the glomerulus was smaller than normal. Here as in the hypertrophic unit a sclerotic but patent interlobular artery gave rise to a greatly thickened afferent vessel which entered the tuft and broke up into a few distorted capillaries. Much connective tissue was seen between the capillaries. Here also, Ludwig's anastomosing branch was not present.(I4)

In the case of the atrophied unit the decrease in the size of the proximal convoluted tubule was definite. It was reduced in diameter and markedly irregular owing to its irregular

constrictions that had been produced by the contracting scar tissue. The question as to whether there was any shortening of the proximal convoluted tubules was for the most part in doubt. In some cases no shortening was believed to have taken place. In these tubules atrophy and regeneration were thought responsible for having replaced the lining with an entirely atypical epithelium.(I4)

Many of the normal size units were found to have a normal appearance. In others the beginning of the destructive process as it has been described in acute glomerulonephritis was noted to be taking place. This was taken as an indication that the kidney was still undergoing the same kind of insult it had in the acute and subacute stages and that the glomeruli were still being destroyed.(I4)

Another interesting demonstration made by Oliver and Lund was that some of the hypertrophied units were found to be aglomerular, being entirely severed by scar tissue from the glomeruli to which they were originally attached. This, of course, meant the tubule was cut off from its blood supply coming through the glomerulus. However, Ludwig's vessel which normally acts as a shunt between the afferent arteriole and the tubular plexus of capillaries, was found to be much enlarged so that the blood supply to the tubule was maintained. There is and old dictum of renal pathology that obliteration of the glomerulus is followed by inactivity, atrophy, and collapse of the tubule. In this case the dictum does not hold true. The distended lumen gave evidence that some sort of fluid was contained within it. In lower forms of animal life with aglomerular kidneys, the tubule is able to perform varied functional

activities. It is not beyond the realm of possibility that it does so to some degree under pathologic conditions in the mammalian organ. Grafflin has shown that at least one fish, the daddy sculpin, begins life with glomeruli which gradually undergo degeneration, so that the adult nephrons are aglomerular.(I4) (20)

The blood vessels are thickened in this kidney. Vascular sclerosis takes place. Fishberg has shown that in this condition the lesions are similar to those met with in essential hypertension, and may be as severe in degree. In the small arteries a diffuse hyperplastic sclerosis characterixed by a hyaline thickening of the intima, and a splitting or reduplication of the internal elastic lamina takes place. In the arterioles an endarteritis obliterans occurs. This consists of a proliferation of the connective tissue of the intima with resulting narrowing of the lumen. This change is probably caused, at least in part, by obstruction of blood flow through the damaged glomeruli.(I5) (I6)

With this destruction of the nephron and the vascular supply to the kidney the parenchymatous tissue is gradually replaced by white fibrous connective tissue. The end result is a scarred and contracted kidney.(I5)

Attempts were made to estimate the percentage of glomeruli destroyed and the percentage functioning in cases terminating with chronic glomerulonephritis. It was calculated by counting the epithelial crests and hyaline areas where the glomeruli were destroyed and comparing these with the number of functional units

present in a section. This was proved to be unreliable by Moritz and Hayman who have shown that a large number of glomeruli when destroyed disappear completely and blend with the surrounding connective tissue so that not even a scar may be detectable. These men estimated as many as three-quarters of the glomeruli may disappear without leaving recognizable scars and still the kidney would be able to function to some extent. This is a valuable fact to bear in mind in examining sections of a kidney in chronic glomerulonephritis.(I8)

The pathological process of glomerulonephritis is a dynamic one. While we group it into three stages clinically the pathological process is a continuous one which has as its end result the destruction of the nephron and its replacemant by fibrous connective tissue. The hypertrophied units found in the latter stages of the process probably represent an attempt on the part of the kidney to compensate for the destruction in numbers of nephrons by an increase in size of the individual units. While a typical lesion has been described for each stage of this disease it should be born in mind that the glomeruli are hardly ever all involved to the same degree at any time. Lesions typical of one stage are at the same time practically always found also in a more advanced stage.(I4) (2I)

A discussion of the course of the pathological process deserves mention. An acute glomerulonephritis that is not severe enough to terminate life at once may go into the subacute stage and produce

death from uremia in a few months. Here a considerable number of nephrons are involved at the same time and the pathological process is what might be termed a fairly active one but it is less severe than in a case terminating in the first stage.(25)

There is another type in which an acute nephritis is manifested but in which the clinical symptoms mostly resolve only to culminate in chronic nephritis after a number of years. In fact this is often the case. Here the pathological process is explained as that in which there is some degree of recovery but it is incomplete. A number of nephrons are being involved and destroyed all the time. The process is not severe enough to give the clinical manifestations of a subacute glomerulonephritis, but to all appearances the patient has recovered only to succumb a few years hence with the symptoms of a chronic nephritis. It is easy to understand how such a pathological process involving only a small number of units at a time could continue when one considers that fifty per cent of the nephrons of the normal kidney have to be destroyed before any signs are noted.(25)

It has also been shown that the number of glomeruli acutely involved by the pathological process described may be minimal so that the symptoms of an acute or subacute nephritis are not manifested. Because of the gradual destruction of nephrons, the case comes to the doctor's attention with the symptoms of a chronic nephritis. Such a thing is not difficult to understand if we will remember that involvement of the nephrons in the pathological

process of glomerulonephritis can be over a wide range both as to number and intensity. Moreover this process can go on over a number of years gradually destroying more and more of the functional units of the kidney.(25)

SIGNS AND SYMPTOMS

The signs and symptoms of glomerulonephritis, i. e., the means by which we recognize the disease, are varied. They also tend to vary from time to time and are by no means constant.

No consideration of this phase of the subject is complete without reference to Bright's work. His original article on the history and symptoms is quoted: "A child, or an adult, is affected with scarlatina, or some other acute disease, or has indulged in the intemperate use of ardent spirits for a series of months or years: he is exposed to some causal 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 edematous. If he happen, in this condition, to fall under the care of a practitioner, who suspects the nature of his disease, it is found that already his urine contains a notable quantity of albumin: his pulse is full and hard, his skin dry, he often has headache, 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 causal of 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 countenence becomes bloated; or the calls to micturition disturb the night't repose. After a time, the healthy color 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 steal 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 albumin, 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 serum is milky and opaque; and nice analysis will frequently detect a great deficiency of albumin, and sometimes manifest indications of the presence of urea. If the disease is not suspected, the liver, the stomach, of the brain divide the care of the practitioner, sometimes drawing him away entirely from the more important seat of 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 it 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 edematous, and, in a state of asphyxia or coma, he sinks into the grave; or a sudden effusion of serum into the glottis closes the

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 recurrence of his symptoms; or again, almost dismissing the recollection of his ailment, he is suddenly seized with an acute attack of pericarditis, or with a still more actue attack of peritonitis, which, without any renewed warning, deprives him, in eight and forty 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, worne out by convulsions, or overwhelmed by coma, the painful history of his disease is closed".(36)

The general course of the ailment as well as the complications can hardly be better described at the present time than they were by Dr. Richard Bright in the above. He was not only familiar with the general course of the ailment, the occurence of a terminal pericarditis or peritonitis, and the disturbances of vision, but also with the rise in the blood urea, the reduction in serum albumin, and the lipemia. This is all the more marvelous since it was one-hundred years before the age of blood chemistry. Another important consideration is that even lacking the instruments necessary for an accurate estimation of the blood pressure, he noted the hard pulse and the gradually increasing pallor. Some men live ahead of their times. This can certainly be said of Dr. Richard

Bright [illegible] the present

Bright. Even with the instruments and knowledge of the present time we can go little beyond his explanations.(20)

However, to adequately understand our subject from the symptom standpoint, we need to consider glomerulonephritis in its three stages. It is necessary to keep in mind all the time that these three stages blend one with another. There is no defined boundaries or limitations either here or in the pathology.(20)

Acute diffuse glomerulonephritis is generally proceeded by some other acute infection. The onset of the renal symptoms apparently varies with the type of infection. In the post-tonsillitis cases the onset occurs at about the tenth day. Those following scarlet fever occur during convalescence, on an average between the fifteenth and twentieth day. The development of edema, first involving the upper eye-lids and face, may be the first objective symptom. It is usually accompanied by headache, nausea or vomiting, slowing of the heart and respiratory rates, blurring of vision, and elevation of systolic blood pressure to one-hundred and forty, one-hundred and sixty, or higher. Generally the blood pressure does not rise above one-hundred and eighty. The localized edema may be followed by accumulation of fluid in the chest and abdominal cavity. The eyegrounds may show edema of the optic disk, but retinal hemorrhages or exudates rarely occur. The urinary output is decreased and the urine contains abundant albumin, red blood cells, leucocytes, and epithelial, granular, and blood cell casts. The casts are particularly abundant. Blood

in the urine is generally the most striking abnormality that alarms the patient. The urine is usually acid in reaction, in which case the color is smoky or brown from hematin. If it is an alkaline urine, the color will be red from hemogloblin. The excretion of urea is diminished; and, in the presence of edema, the excretion of chlorides is also decreased.(33) (37)

The non-protein nitrogen in the blood is but slightly increased to thirty-five or forty mg. per cent. In patients progressing unfavorably these figures may be much increased. At death it averaged one-hundred and twenty-five mg. per cent in a number of cases. In acute glomerulonephritis a leucocytosis is not uncommon. This may be ascribed in some cases to such complications as otitis media or bronchopneumonia. The acute stage may continue for a number of weeks and result in recovery with surprisingly little evidence of damage. Recovery is usually the rule. While this varies generally there is complete recovery in ninety per cent of the cases.(27) (37) A slow heart and pulse rate is characteristic in the acute stage of glomerulonephritis. If the heart rate is accelerated and if the hypertension is marked, the possible occurence of convulsive seizures should be borne in mind, The presence of increased blood pressure has seemed to be definitely associated with cerebral edema.(37)

Mention needs to be made of the difference in the manner of onset of acute glomerulonephritis. In children the onset may be sudden with a sharp rise of temperature, headache and vomiting,

edema of the face, oliguria and a convulsive seizure. This is often the severe reaction young children have. In other cases two or three weeks after some acute gastro-intestinal infection, it will be noticed the child appears pallid and fretful, has a poor appetite and vomits frequently. In infancy and childhood, contrary to the cases in adults, the heart rate is increased. In children anemia tends to develop rapidly. Other than this the acute nephritis is about the same as in adults.(29)

The subacute or nephrotic stage of glomerulonephritis is characterized by marked edema. As previously mentioned, this has been called the wet stage of nephritis. There is also a moderate anemia, marked albuminuria, hematuria, decreased urinary output, hypertension of moderate or marked degree, and abnormal blood nitrogen at times. These cases may go directly into uremia or pass to the chronic and terminal stages of the disease.(37)

In this stage a rather massive edema is generally present. The face is considerably swollen. Often there develops ascites and hydrothorax. This edema is associated with a reversal of the albumin-globulin ratio. When the plasma proteins fall below four and five-tenths gram per cent edema is likely to develop. With this edema there is an abnormal blood cholesterol of three-hundred to three-hundred and fifty mg. per cent. Normal blood cholesterol is one-hundred and forty to one-hundred and seventy mg. per cent. Retention of chlorides in the tissues occurs. Other symptoms of importance are headache, anorexia, gastric disturbances,

dyspnea, epistaxis, and asthenia. If the case approaches the end, the symptoms of impending uremia, such as vomiting and mental confusion may be the first that lead the patient to consult a physician. In the majority of cases the patient's most prominent symptom is the presence of edema with albuminuria which may continue with periods of retrogression and variable improvement for months or years.(29) (32) (37)

In patients near death the blood non-protein nitrogen generally varies from one-hundred to two-hundred mg. per cent. The creatinine retention in a series of cases averaged six mg. per cent. The anemia in this stage is generally not marked.(37)

The quantity of urine at this point is generally decreased and hematuria is more or less constantly present. There are still the casts in the urine described in the acute stage. Generally they are not quite so numerous. In fatal cases, as the terminating point nears, large "renal failure" casts appear in the urine. These casts are short, dark, abnormally broad structures with squared-off ends. They occur in uremia, and therefore have a very important significance as to the prognosis of a case. Addis has demonstrated by sections that they are formed in the ducts of Belleni.(2I) The blood pressure is generally high in these cases often being above two-hundred mm. systolic pressure.(33)

Chronic glomerulonephritis has the clinical symptoms of headaches, indigestion, muscular weakness, and visual disturbances. On examination marked anemia, hypertension, albuminuria, hematuria, and abnormal blood nitrogen retention are occasionally found. These

symptoms all vary considerably. There may be a varied amount of edema but in the chronic stage generally there is none.(37)

As was mentioned in the chapter on etiology a history of preceeding attacks suggestive of earlier kidney disturbance is strangely lacking in many patients. This must mean that the attacked producing the initial damage was slight and produced few symptoms; that the subsequent progress was so gradual over a period of years that the second stage likewise escaped attention and only in the last stage is the disease making itself known. Most cases in the third stage only seek attention when renal insufficiency with its symptoms sets in. In these patients hypertension is a frequent occurence but in only about one-third of the cases does the systolic blood pressure exceed two-hundred mm. and the diastolic pressure exceed one-hundred and thirty mm. This is in great contrast to nephrosclerosis where the large majority of patients have hypertension.(37)

Marked blood nitrogen retention is a constant symptom in most patients. The non-protein nitrogen in the great majority of cases is above one-hundred mg. per cent and may be two-hundred mg. per cent or over. As high as three-hundred and eighty-four mg. per cent has been recorded. The average creatinine retention in a series of patients was eight mg. per cent.(37) (I3)

A secondary type of anemis has always been an important symptom in chronic glomerulonephritis. The skin has a peculiar pasty pallor. Decreased bone marrow function and the continued loss of blood cells in the urine, in varying quantities over long periods

of time, must be considered among the causative factors. The anemia bears no relationship to the presence or absence of edema. Bleeding from the gums or nose, metrorrhagia and menorrhagia, or bleeding from the intestinal tract is a relatively common symptom. The degree of anemia usually parallels the extent of the abnormal nitrogen retention and may be used as an estimation of the severity of the patient's condition. In occasional cases in the terminal stage the anemia may be the most outstanding manifestation of the disease.(26) (37) (I3)

There is always albuminuria but it is often not noteworthy. Casts are not so plentiful as they were in the earlier stages of the disease. As some men remark, the kidney has lost its ability to form casts. The hematuria of this stage may be from slight to moderate. The specific gravity of the urine depends on the ability of the kidney to excrete nitrogenous waste products but is generally below I.0I5 and fixed within a rather narrow range. The urine is often scant. All this is not surprising when it is remembered that this is a stage of renal failure.(I3)

The kidney also fails in the production of ammonia and the excretion of organic acids. In this lack of function it fails to maintain the acid-base balance of the plasma. This allows an acidosis to take place in the uremic syndrome.(35)

As renal efficiency approaches zero the individual begins to complain of headache, loss of appetite, nausea, and vomiting, and

this is followed by drowsiness, convulsions and coma. During this coma death generally takes place. With the exception of the uremia of an acute nephritis, it is doubtful whether an individual can recover, except very temporarily, from the syndrome of true uremia. At best one is certain life will yield before long.(27)

THE URINE

In acute glomerulonephritis hematuria is an important symptom of the disease. The urine may have a hazy, smoky, or bloody appearance, or the red cells may only be seen in the sediment. Albumin is constantly present throughout the course of the disease. The amount of albumin usually varies between one and ten grams per liter, but may reach twenty grams. At the beginning of the disease the quantity of urine is diminished to a few hundred cubic centimeters in twenty-four hours, or it may be entirely suppressed. Cases with complete anuria at the beginning usually have a fatal outcome. In cases with a more favorable prognosis the daily output gradually increases. The sediment shows hyaline, granular, and blood casts. In the early stage they are numerous, but with improvement they tend to become fewer in number. Red cells, leucocytes and epithelial cells, which often contain fatty granules, are also seen in the sediment.(31) There is usually no interference with the ability of the kidneys to concentrate in acute nephritis and consequently the specific gravity of the urine is, as a rule, maintained at normal levels. A moderate number of leucocytes are usually present in the urinary sediment but frank pus is not encountered. The most characteristic and important elements diagnostically are red blood casts if present among the formed elements in the urine. The urine, if edema is present, is also generally deficient in sodium chloride output. As the disease process begins to resolve the albuminuria is

frequently the last manifestation to disappear in the process of healing.(38)

With subacute nephritis the symptoms of the acute stage may gradually disappear but the albuminuria, casts and red cells persist in varying amounts. The hematuria is also quite variable. The albuminuria is generally large in amount. There is retention of chlorides in the tissues and their consequent absence in the urine. The quantity of urine is usually decreased; the specific gravity, depending upon the amount of urine excreted, is usually increased; and hematuria is more or less constantly present. Almost always there is a considerable number of epithelial cells and cellular casts in the urine. If the case begins to approach renal failure the large "renal failure" casts described by Addis appear in the urine. These are short, broad casts with square ends and are dark colored. The urine should be carefully examined for them because they are absolutely indicative of uremia and imply a fatal outcome for the case.(2I) (37)

In chronic glomerulonephritis about the earliest indication of the process is a constant often slight albuminuria, a few hyaline casts, leucocytes, and red blood cells in the urinary sediment. With superimposed acute attacks the urine shows more red cells. At first the quantity of urine is normal; later it may be diminished in cases that show some edema, or become increased as the edema clears. Nocturia, three or four times each night, may be

a prominent symptom. The color of the urine becomes pale; the specific gravity, at first high and varying with the quantity of urine, later becomes lower and ultimately tends to become fixed at about I.OIO. The night urine tends to approach the day in volume output and may be more. This urine appears much as a watery solution, the kidney having lost its ability to excrete urochrome. The casts are distinctly less numerous at this stage. As renal failure approaches the "renal failure" casts previously described appear. Then the case soon terminates in uremia.(3I) (2I) (37)

Lately there has been considerable question raised concerning the reason for and nature of the protein in the urine, Some work has been done on this subject which deserves consideration if for no other reason than to show the confused state of affairs at the present time. The question has been raised as to why the kidney is unable to excrete water and salt in certain stages of nephritis but can always excrete albumin. Furthermore it has been claimed pure renal insufficiency does not produce the clinical picture of nephritis. The death of animals after removal of the kidneys is not at all like the death caused by nephritis. Common observation doubts the reasoning of Thomas because he fails to take into consideration the time during which nephritis acts to produce its effects when compared to the short span until death when the kidneys are removed. Nevertheless some constructive ideas do appear in this article. If water and salt cannot pass through the glomerulus

how can a large molecule the size of albumin do it ? He believes the reason water and salt are not excreted is because they are taken up and held by the tissues; in other words, that the primary trouble is in the tissues and not in the kidneys.(28)

In an experiment with dogs it has been shown that foreign proteins are excreted rapidly through the kidneys if they are injected into the blood stream. From this Thomas has assumed the hypothesis that either a normal or damaged kidney is able to retain the normal body proteins in the blood. Only when proteins have become so altered that they no longer conform to the requirements of the particular organism, are they treated as foreign proteins and excreted. He believes that due to a condition in the tissues a breaking up of proteins into proteose and peptone radicals occurs. These radicals attach themselves to the albumin molecules and are excreted. Some experimental work in which peptone was injected into dogs and appeared in the urine conjugated with albumin molecules was also presented. He also believes chemical work on the proteins excreted in nephritis indicates this same thing.(28)

Another observation made was that the cystine content of the protein fraction in the plasma remaining after precipitation of the globulins in patients with the nephrotic syndrome was lower than the cystine content of normal serum albumin. This protein fraction could be saparated into two parts. One appeared to be the same as normal serum albumin, for it had the same cystine content, the other contained far less cystine than does serum albumin or any

serum globulin fraction. When the globulin in the urine of these patients was precipitated it was found that the cystine content of the remaining protein was higher than that of the corresponding fraction of the plasma, but lower that that of normal serum albumin. The substance with low cystine content, therefore, appeared to pass through the nephrotic kidney less readily than does serum albumin.(34)

These two recent works are presented to show that there is some indication of change in the serum proteins in nephritis, and that it may be these altered proteins which are excreted.

THE OCULAR FUNDUS

In any consideration of diseases which directly or indirectly affect the vascular system we must not forget to consider the ocular fundus. The retina and underlying choroid are highly vascular tissues. Here any disturbance of the general organism may be noticed before the disease process has progressed far enough to produce noticeable pathology in the less delicate tissues of the body.(46)

Albuminuric retinitis is what the retinopathy associated with all forms of nephritis is called. This is a confusing and misleading term that should be dropped, since it is generally agreed that albumin has nothing to do with the retinitis. The condition is most commonly associated with chronic nephritis but may occasionally be found in the acute and subacute cases. Between twenty and thirty per cent of cases of chronic nephritis develop it while it appears that less than five per cent of the cases of acute and subacute nephritis have it.(43) (47)

The retinal changes which may be found in a case of albuminuric retinitis may include some or all of the following: (I) Optic neuritis and retinal edema, which are shown by a blurring and indistinctness of the disc margins, first on the nasal side, the temporal border being the last affected. The retinal edema may extend from two to four disc diameters from the disc margins. (2) Hemorrhages which may be either striate or punctate in character, and are usually situated in the nerve-fiber layer of the retina.

(3) Exudates ("cotton-wool patches") which are irregular in size and shape. (4) Small white spots may be found in the macular region. These are situated in the deeper layers of the retina, and are found more frequently than the so-called (5) "star figure" in the macula which is due to fatty deposits along the fibers of the retina. (6) The blood vessels may show increased white stripes along the course of the arteries. The veins may appear distended while the arteries seem underfilled. (7) The blurring of the optic neuritis may become so marked as to simulate a choked disc, especially when there is an associated edema of the optic nerve. (8) Detachment of the retina may occur in the more advanced stages of the disease. (9) Of these the most common pathological signs are the small white spots, the cotton-wool patches (sometimes called snowbank exudates), the papilledema, and the "star figure" in the macula.(46)

In general, all the changes in the retina and its vessels, so far as they are incident to hypertension and renal disease, are primarily due to the hypertension because without this they do not occur. However, many believe this is not the only factor. Grave destruction of the kidneys as seen not only in glomerulonephritis but also in renal tuberculosis, septic kidneys and renal tumors, do not cause any abnormality of fundi unless hypertension develops. Neither hypertension nor retinitis is usually found in children with glomerulonephritis nor in persons with glomerulonephritis as a complication of bacterial endocarditis. Similarly, changes in

the retinal tissue itself are not seen in cases of advanced arteriosclerosis without hypertension.(4I) (42)

A belief has been expressed that the retinitis is probably due to a toxin circulating in the blood as a result of the kidney involvement. This is hard to prove, however, because it has been noted that the degree of retinitis bears no fixed relationship to the nature or severity of the renal pathology. The retinitis is nearly always bilateral in nephritis, while in arteriosclerosis it is unilateral in fifty per cent of cases according to Douglas.(43)

If chronic parenchymatous nephritis is contrasted with chronic interstitial nephritis in the former one sees in the fundus cotton-wool patches, retinal edema, sometimes retinal detachment, occasionally a few hemorrhages but no star figure. In chronic interstitial nephritis on the other hand the retinal vessels are found sclerosed, with many hemorrhages, and a star figure at the macula.(43) The most important retinal findings, according to Fishberg, that form renal or albuminuric retinitis are cotton-wool patches and papilledema. The other lesions described usually co-exist.(39)

The retinitis of arteriosclerosis is distinguished from renal retinitis mostly by a tortuosity of the vessels, constrictions of the veins where the arteries pass over them and often an irregularity of the caliber of the lumen. Exudates may sometimes be seen in the macular region. These consist usually of a few almost snow-white, round spots with a sharply defined margin.(48) This is the

classical description of arteriosclerotic retinitis and one which can easily be distinguished from renal retinitis. However, Floyd mentions cases where the different stages between an arteriosclerotic and a renal retinitis have been observed.(38) (41)

The pathology of renal retinitis has proved to be a difficult one and until late it has not been satisfactorily worked out. The cotton-wool patches are histologically composed of fibrous material which in the later stages becomes hyaline. They may lie in the whole thickness of the retina but predominate in Henle's layer. A "star figure" or a fan-shaped figure is formed of small rod-like exudates. Although present in other conditions, they are most commonly found in renal retinitis. The individual spots composing the star are densely white with a sharply defined edge. They are sometimes preceeded by a series of very faint radiating lines in the same situation suggestive of folds or lines of tension in the retina. These exudates are believed to be composed of hyaline material or patches of varicose nerve fibers.(40) (48)

The papilledema has been the subject of considerable question in renal retinitis. It is believed this is due to increased intracranial pressure. The rise in blood pressure increases the intracranial pressure. Frankly this explanation has been opened to question. Few cases of hypertension have a papilledema. The retinal edema here is quite certainly believed by authorities to be due to the engorgement of the arteries and veins seen in this condition.(44) (45) (48)

Renal retinitis, except in the case of acute nephritis, has a very grave prognosis. Most authorities give two years as the outside

limit of life expectancy. Douglas mentions that of his patients with renal retinitis sixty-five per cent were dead within a year and all within two years.(43) Bulson believes three years is the limit of life expectancy from the time the lesions first appear.(44) Ball states that probably eighty-five per cent of all patients with renal retinitis die within two years. Fellows observed three cases with renal retinitis brought on by failing kidneys during pregnancy. These were the only cases in his series that recovered. (46)

EDEMA

The interstitial fluids are kept constant in the normal body by a remarkable balance between the physical pressure of the blood in the capillaries, derived primarily from the heart beat, and the osmotic pressure of the plasma, derived essentially from its proteins. This is the famous hypothesis suggested by Starling. It has stood the test of time. In detail the theory is that at the arterial end of the capillary the physical pressure exceeds the osmotic so that fluid moves out into the tissues. At the venous end of the capillary the osmotic pressure is increased by the concentration of the plasma resulting from its loss of water, and the physical pressure is decreased for similar reasons, so that fluid then passes back into the capillary. The net result of dynamic equilibrium between filteration and reabsorption is the maintainance, in the normal person of a constant water content in the intercellular spaces. However, even in the essentially healthy body this equilibrium can be disturbed. Standing for long periods of time will produce a slight edema at the ankles.(49) (52)

This osmotic pressure can be measured fairly accurately by analysis of the serum proteins of the blood. Factors are known whereby the percentages of albumin and globulin may be translated accurately into osmotic pressure as millimeters of mercury. However, simple protein percentages are sufficient for clinical use.(54)

The hydrostatic pressure in the capillary is difficult to

determine experimentally and almost impossible clinically. The nearest approach at the bedside has been by means of inference based on the venous pressure.(54)

After illustrating the fine equilibrium that exists between filteration and reabsorption, it is not difficult to understand that any factor which interferes with the reabsorption of fluids from the tissues will produce an edema.(52)

The edema of acute glomerulonephritis is the most difficult and unsatisfactory type to understand in the light of our present knowledge. This type of edema is sudden in onset and confined mostly to the loose aerolar tissues of the body. It is an edema widely distributed. The sudden onset of this has lead many clinicians to suggest that the edema is due to capillary damage. The most important evidence along this line is the high protein content of the edema fluid. This has lead to the suggestion that the capillaries are damaged.(50)

Another hypothesis concerning the edema of acute glomerulonephritis holds that there are profound changes in the capillary blood pressure. In other words the physical pressure forcing the edema fluid into the tissues is increased in acute nephritis. To support this we have the evidence that there is generally a moderate rise in blood pressure in the disease. Direct measurements of the capillary pressure have given varying results due principally to the crudeness of the methods. Accurate study of arteriolar and venous pressure would probably add considerable to what is known about this. Further work is indicated.(50)

Evidence has been presented to show that there is chloride retention in the tissues at this stage of the disease. When edema is present the chlorides of the plasma have been found lowered and the chloride output in the urine is also reduced. This indicates chlorides are being held in the tissues, increasing the osmotic pressure there, and probably playing a part in the production of edema.(55)

The edema of subacute glomerulonephritis, sometimes called the "wet" stage of nephritis, is probably the most clearly understood. Dr. Richard Bright in 1827 pointed out that the plasma in nephritis is often poor in protein. Epstein in 1917 first called attention to the application of the Starling hypothesis to this. Epstein showed that a low serum protein implied a lowered osmotic pressure and that this equilibrium was altered in such a manner favorable to the collection of fluid in the tissue spaces. It was later proved that this decrease in protein is almost exclusively in the albumin fraction so that the normal albumin-globulin ratio is reversed. Another fact of great value is that since the albumin molecule is much smaller than the various globulin molecules it exerts a proportionately higher osmotic pressure. Its loss from the blood causes an even more serious dimunition in plasma osmotic pressure than was suspected in the originally observed decrease in total protein. Barker and Kirk, working in Christian's laboratory, by means of plasmaphoresis have shown that when the

albumin-globulin ratio becomes reversed and falls below a certain critical level edema ensues without fail. This piece of work more than any other has served to put our understanding of the cause of edema in subacute nephritis on a firm basis. In other words, it appears without doubt to be due to the loss in proteins (mostly albumin) and the consequent lowering of the plasma's osmotic pressure. While this is probably not the whole explanation it does play a large part. This loss of protein, according to the Starling hypothesis, results in a diminished reabsorption of fluids into the capillaries from the interstitial tissues and edema is the result.(53) (55((52)

The edema of subacute nephritis is often extensive. Nearly every tissue in the body may be swollen and water-logged. Even ascites may accompany it. Here we have considerable salt retention in the tissues. The salt retention is most marked at this stage of glomerulonephritis. In this stage the clinician is often called on to relieve the discomfort produced by this widespread edema.(5I)

Chronic glomerulonephritis often reaches the uremic or preuremic stage without edema formation, in fact dehydration is a more common complication with uremia. If edema does appear it is rarely extensive and may be the result of several mechanisms.(5I)

A decreased plasma osmotic pressure may occur in the uremic stage of chronic glomerulonephritis, and the degree of disturbance may be told by a study of the serum proteins. Here the mechanism

of edema production is the same as in the edema of subacute glomerulonephritis. At this stage we can also have an edema due to anorexia or vomiting. This is really what might be termed a war or starvation edema. In this case the plasma proteins are so depleted by starvation that they are unable to maintain the plasma's osmotic pressure for reabsorption of fluid from the interstitial tissues. Another common thing that must not be overlooked in chronic glomerulonephritis is that often the heart is involved and we may be comfronted with a dependent edema of cardiac origin. The edema here is due to a slowing of the circulation in dependent parts and a consequent failure of reabsorption from the interstitial tissues.(52) (55)

While a description of the edema in chronic glomerulonephritis has been given, it should be carefully pointed out that this stage generally has no edema. The skin is usually dry and dehydrated. This is a stage of uremia and kidney failure.(20)

UREMIA

True uremia has been defined as a toxemia developing in the course of nephritis or in conditions associated with anuria. Bright himself gave it this name because of his observation of an increase in the urea content of the blood in this toxemia. He regarded urea as a highly toxic substance. While we know at the present time this is not the case, no one is quite sure what the toxin is. Many substances have been suggested.(20)

Death from uremia may occur in the first or acute stage of glomerulonephritis, seldom in the second stage known as the "wet" form of nephritis, and very frequently in the third stage, which indeed it forms the inevitable conclusion if some intercurrent malady or complication does not produce death. The state of complete anuria, from whatever cause, does not result in the uremic syndrome. The symptoms of anuria, whether in man or in experimental animals, are progressive asthenia, anorexia, and stupor ending in death. Such a condition should be called urinary poisoning rather than uremia.(20)

The essential symptoms of true uremia are as follows: (I) General mental and bodily fatigue, weakness, drowsiness, and a dullness which Widal designated as veritable narcosis. (2) Excitation phenomena; muscular contractions, tendon jumping, an increase in the skin reflexes, narrowing of the pupils, and deep breathing. (3) Rapid loss in weight and decrease in muscle mass.

(4) Dyspeptic symptoms, loss of appetite, hiccoughs, vomiting. (5) Tendency to inflammation and necrosis, laryngitis, pharyngitis, stomatitis, gastritis, enteritis, necrotic ulcers of the mouth, stomach, intestinal mucosa and the skin and, in addition, pericarditis. (6) Drop in temperature. (7) Odor of urine from the breath. (8) Absence of convulsions and headaches. The picture is always the same although not always complete as to symptoms. The condition is ushered in by various ways. In some cases the dyspeptic symptoms are in the background while in others the diagnosis of uremia may be missed because they form so prominent a part of the picture. In some cases muscular contractions never occur. In others deep breathing predominates. Asthenia seems to be the most constant symptom.(I3)

The urea concentration in the blood can be increased to one-thousand mg. per cent in cases of renal insufficiency before any symptoms are produced. It quite conclusively proves that urea in itself and alone is not the cause of uremia. There is another fact, however, which should not be lost sight of. Urea is known to increase cell membrane permeability. This may thus allow substances which are toxic to pass more rapidly and easily through the tissues. (60)

In uremia the products of protein putrefaction of the intestines are increased in the blood. Obermayer and Popper noticed the odor of the serum in uremia and observed fecal odor from the distillate of uremic blood. The serum odor might be considered the simplest and finest test of uremia. The diazo test of Andrewes' has also been used. Harrison and Broomfield have made

almost certain proof that the reaction is due to indican or possibly in part to indoxyl glycuronate. A fact of note is that indican does not pass into the cerebro-spinal fluid. There are reasons to look upon indican and its mother substances, indol and indoxyl, as relatively non-toxic. Cases are illustrated with a relatively high indican contnet of the blood which were comparatively well.(58) (59)

Volhard believes a different situation to prevail in regard to the phenol derivatives. He believes no blood test gives a better basis for prognosis in renal insufficiency than Becher's xantho-proteic reaction, which informs us as to the degree of retention of aromatic substances in general. Volhard sites cases to prove that the uremic symptoms do not parallel the retention of urea, but rather of the aromatic substances in the blood. Generally when the xanthoproteic value reaches eighty symptoms of uremia occur. Becher, working in Volhard's laboratory removed the intestines in rabbits;, they survived the operation ten hours. The animals produced a water clear urine free from phenols, indican, and urochromogen, and following the extipation of the kidneys no indican was found in the blood. Volhard observed a number of patients in his clinic in Halle and Frankfort. Not a single instance of true uremia developed without elevated phenol values or a strong qualitative xanthoproteic reaction. Becher pointed out that the symptoms of uremia- fatigue, insomnia, loss of weight, gastro-intestinal symptoms, drop in temperature, vomiting, skin symptoms, cachexia- remind on of the symptoms.found among workmen in carbolic acid factories. Perhaps,

Volhard also believes, the final decrease in kidney function might be explained by injuries due to phenols.(I3)

Magnesium is a rather debatable subject in uremia. We know there is an accumulation of it. This particular ion is known to have a depressive effect on the nervous system. This may help to account for the mental apathy and coma.(56)

That potassium is increased we definitely know. It acts as an irritant to the central nervous system and is probably a contributory factor in promoting the irritative phenomena.(56)

For some unknown reason the calcium is decreased in uremia. This decrease is in the ionized calcium. Although the cause is unknown, oxalates and citrates have both been suggested. The fact that increased phosphates occur in uremia may be an explanatory factor here since they tend to, by uniting with it, decrease the ionized calcium. As calcium is hnown to lessen nerve irritability its absence probably also helps to promote the irritative phenomena.(56)

Volhard feels compelled to assign an important role in the production of the uremic picture to the retention of products of intestinal putrefaction. So far, the xanthoproteic reaction, which perhaps chiefly depends upon retention of such products, is the only chemical reaction of the blood which runs parallel with the degree of uremic intoxication. We should not forget the classical experiments of Magnus Alsleben which have shown that the intestines represent the greatest source of toxins in the organism.(I3)

Acidosis must be considered in uremia. While it is not always present it is often an accompanying complication. There is certainly no relation between the urea retention and acidosis. The factors which have to be considered in relation to the cause of this acidosis are: (I) Inability to form ammonia in consequence of renal pathology. (2) Retention of inorganic acid valencies consequent upon renal insufficiency and a preponderance of the disturbance of acid versus alkali section. (3) Abnormal production or retention of roganic acids. We are certain acidosis is not founded upon a disturbed formation of ammonia. If it were all nephritics would remain free of uremic acidosis on a basic diet. Large administration of alkalies does not help the situation.(I3)

A rather strange finding concerning acidosis has appeared. A bicarbonate deficiency is nearly always found. The bicarbonate may be reduced to four-fifths of its normal value. The chlorides are also most usually found to be decreased. This decrease may reach twenty to thirty per cent below normal. Another base-binding plasma constituent which exceptionally may remain normal but which will usually be found markedly reduced and never increased is the plasma proteins. Reductions of fifty per cent and more may be found in plasma proteins in uremia.(I3)

These three acid components of the plasma just discussed, normally are equivalent to about ninety-five per cent of the total base. With these acid components decreased it is evident that the acidosis present must either be due to a decrease in the base or an increase in organic acid radicals.(I3)

By quantitative tests of the total fixed base is has been found that this is seldom increased but most generally decreased. With such a reduction we would normally have a decrease in the osmotic pressure of the blood. Here, however, this is not the case. It is normal or increased because of retention of non-electrolytes, particularly urea, which may reach a level of fifty to seventy mg. per cent. Exceptional cases up in the neighborhood of one-hundred and fifty mg. per cent have been recorded.(I3)

We have as yet no satisfactory explanation for this diminution of base. The theory has been advanced that it occurs as a compensatory mechanism to keep the plasma osmotic pressure normal where it would otherwise be increased through the unavoidable retention of the freely diffusible non-electrolytes.(I3)

The identification of the organic acids has been a problem on which little advance has been made. Peters thinks that when they are high the patient has taken little food and suffered from a good deal of vomiting. He once thought of an aliphatic acidosis of the same nature as in diabetes but since then his opinion has changed. This is now looked upon to be due to aromatic oxyacids and he believes there is an aromatic acidosis in uremia in contradistinction to the aliphatic acidosis of diabetes.(57)

Later workers have found these acids in the blood in uremia to be organic ether-soluble acids. By direct quantitative estimation these acids have been found sufficient to account for the anion deficiency. They have also been found to be partly aliphatic and partly aromatic in nature. A portion of them are volatile with

steam distillation. Volhard hopes to be able to show that these acids are not only of intestinal origin but also of a metabolic origin as products of protein katabolism. The old, once almost discarded idea about toxic protein decomposition, may once more find itself reinstated on the strength of new experimental evidence.(13)

TREATMENT

The patient should have the benefit of bed rest as soon as acute nephritis is discovered, no matter how mild the attack may appear to be. The period of rest in bed will depend on the progress of the case, but even in the least severe one, a minimum of from four to six weeks rest is necessary. In the more severe cases rest in bed should be continued until the blood pressure is normal, the edema has disappeared, the albumin in the urine has diminished to a very small amount, and the urine sediments show no red blood cells for a period of at least two weeks. The patient should then be allowed up gradually. Meanwhile the doctor should watch the urinary sediments closely. The appearance of many red cells means a return to bed.(75) (76)

In providing nourishment for such a patient there are two cardinal dietetic principles, (I) limitation of fluids and (2) the avoidance of prolonged underfeeding. In the beginning with the edema in the face, legs, etc., eight-hundred cubic centimeters of fluid in twenty-four hours is correct. With the cessation of diuresis this level may be increased first to one-thousand and then gradually to fifteen-hundred cubic centimeters. Forcing of fluids is not generally practised any more. During the first two or three days a very practical procedure is to give the patient no solid food but merely eight-hundred cubic centimeters of fruit juice, water or milk. Two or three so-called "sugar days" with one-hundred and fifty to two-hundred grams of glucose flavored with

lemon juice makes an excellent start. After this, if there is no nausea, the carbohydrates and other foods can be increased fairly rapidly until the patient is getting a fairly liberal mixed diet, restricted in its fluid and salt content. It is important to keep the amount of salt in the diet low until the edema has disappeared. If all goes well the patient will generally be free of the edema in two weeks. It is absolutely necessary, however, to avoid any prolonged underfeeding. A protein ration of less than sixty grams per day is inadequate for an adult. Except in specific instances where the level of blood nitrogen is high and one must try and reduce it, the optimum protein allowance is one gram per kilogram of body weight. For a few days in an acute nephritis, the diet may be markedly restricted in proteins. This tends to rest the kidney and to rid the blood of excess non-protein nitrogen. This should not be continued for any length of time, however, because it tends to deplete the individual of his body proteins and to produce a secondary anemia.(65) (66) (67) (75)

Most people take ten grams or more of salt daily. Hoyle has pointed out that if edematous patients are restricted to about two grams a day no appreciable fluid retention is likely to result. Most raw foods are poor in salt, but milk, cheese, salted butter, fish, preserved meats and bread are notable exceptions and therefore should be avoided. Salt restriction to only two to four grams of sodium chloride can be obtained if no salt is added to the food in cooking or before eating and if salty foods are excluded. More severe salt restriction can be obtained by using salt free bread.

A diet has been advocated which reduces the urinary chloride excretion to less than five-tenth grams daily. Such severe salt restriction makes the diet unpalatable and the appetite may be completely lost. This can be prevented to some extent by choosing the food carefully, and flavoring with such things as onions, vinegar, mustard, pepper or nutmeg. Prolonged and severe salt restriction sometimes leads to vomiting, headache and pains in the legs. These symptoms may be rapidly relieved by giving as little as two grams of salt.(67)

Diuretics are contra-indicated. Any such therapeutic improvement of kidney function is limited for two reasons. In the first place a large part of the renal parenchyma is often grossly injured and there is no effective means of stimulating the failing kidney by direct action on its cells. In acute nephritis saline and purine diuretics are almost always useless. Mercurial diuretics are dangerous because of the risk of poisoning.(67) Only in marked edema does Christian believe diuretics should be used. If on giving a restricted amount a diuresis does not ensue they should not be tried a second time. He believes, as a rule, diuretics should not be used in acute nephritis.(72) Stone believes, in the presence of abnormal blood nitrogen retention, impending uremia, and acidosis, the intravenous injection of a concentrated twenty-five to fifty per cent glucose solution is indicated for its diuretic effect.(37)

Attempts have been made to treat acute and subacute

glomerulonephritis with streptococcus vaccines. Derick and O'Hare used vaccine prepared from hemolytic streptococci and from streptococcus viridans. These vaccines were used both on patients who were sensitive and non-sensitive to skin tests made with proteins of the organisms. It was noted in acute glomerulonephritis that eighty-three per cent of their patients were sensitive to either the hemolytic or the green streptococci. In subacute glomerulonephritis this percentage was seventy-four while in chronic it was thirty-two per cent. For this vaccination the nucleoprotein portion of the streptococci was used. A total of sixty-seven patients in the various stages of nephritis were vaccinated. The results can be best expressed in O'Hare's words: "Could one have foretold the untreated course of these patients' illnesses, one would be in a position to say definitely whether they have derived any benefit from the treatment. In no instance do we feel that this form of treatment has influenced the course of the disease unfavorably. The most that one can say is that it may have some merit and, if so, that it adds thereby to our armamentarium in the treatment of hemorrhagic nephritis." Obviously, no positive deductions could be drawn that it definitely benefitted the patient. That is the status of the use of vaccines at the present time.(69)

Liver and iron have been suggested for the anemia. Their use has brought varied results. Blood transfusions have also been suggested for this secondary anemia. The reason for this is that a high protein diet in a severe case may raise the non-protein

nitrogen in the blood and produce a uremia in the patient. The transfusion would add formed elements to the blood of the patient without increasing the non-protein nitrogen. It was pointed out that care needs to be practised or injury to the kidneys was believed to result. The transfusions, it seems, controlled the anemia but had no effect on the edema in a series of cases.(61)

Removal of foci of infection has to be considered. Christian believes that since infection has an etiological relationship to acute nephritis, it should be treated adequately as possible. Therefore, due consideration should be given to the eradication of real foci of infection. The indiscriminate removel of teeth and tonsils in such patients, however, is to be deprecated.(72) An investigation was undertaken by Osman at Guy's Hospital in London to determine the value of tonsillectomy on the course of protracted cases of unresolved acute nephritis. For this purpose cases were selected in whom all signs and symptoms of the acute stage had resolved after a few weeks in bed on the usual light diet. There was some residual hematuria and albuminuria which had shown no signs of diminishing any further during the previous two months. Eight cases of this nature were treated by tonsillectomy. The operation proved of obvious benefit in one case. In this case there was no clinical evidence that the nephritis was causally associated with the presence of diseased tonsils, although the severed tissues were found to be mildly infected.

In the remaining cases tonsillectomy did not seem to influence the course of the disease in any respect. In one case it actually appeared to have precipitated an exacerbation. The conclusion was that tonsillectomy is rarely of value in hastening recovery in cases of unresolved acute nephritis.(68) However, inspite of these results Evans states his belief from the results of a long practise that a careful search for foci of infection should be made in all patients with nephritis. Inflammed tonsils, septic teeth, pyorrhea, otitis media, and impetigo are common findings. These foci should be removed surgically if necessary. In general it is best to wait until the more serious signs of the attack of nephritis have quieted down because an acute exacerbation sometimes follows operation. However, if the condition caused by the focus of infection is severe surgical intervention should not be delayed.(76)

Stone states that in twenty per cent of his cases of acute nephritis convulsive seizures developed. For their treatment he reccomends relaxation in a hot bath or the use of hot packs. The use of two-tenth cubic centimeters of a twenty-five per cent solution of magnesium sulphate per kilogram of body weight, or of five-tenth cubic centimeters of a ten per cent solution per kilogram of body weight intravenously is recommended.(37)

Sweating as a treatment for uremia whether in acute or chronic glomerulonephritis is no longer recommended. Christian believes the frequent sweating of patients reduces their strength and in the end accomplishes very little.(72)

The question arises concerning the termination of bed rest in cases of so called "unresolved" acute nephritis. Months in bed without symptoms try the patience of the sick one, his family and the doctor. If after weeks in bed the only abnormality is the persistence of five to ten red blood cells per high power field, he might be permitted up, especially if the doctor has reason to suspect that this attack is merely an exacerbation of a chronic condition. In these cases one need expect no cure. A normal blood sedimentation rate then is helpful in determining the earliest safe time for the patient to get up.(75)

When the patient is allowed up from an attacked of acute nephritis care must be taken to avoid infections and chills. After precautions include the wearing of warm clothing and the forbidding of cold bathing. If there are no residual manifestations, with the exception of a slight albuminuria, no dietetic restrictions are indicated. Small amounts of albumin in the urine may occasionally persist for weeks or even months, and then completely disappear. An early morning specimen of urine should be examined, because what is sometimes thought to be a persistent albuminuria may really be an orthostatic albuminuria; this is not infrequent in children. No further treatment is usually necessary unless there are residual signs, such as persistent edema, hypertension and albuminuria, which indicate that the disease is passing into the chronic stage.(72) (75) (76)

In subacute glomerulonephritis the edema has been fairly well

studied. It is due, at least in part, to the serum albumin loss in the urine. In these cases an attempt is made to nourish in such a way as to cover the protein loss in the urine as well as to meet the metabolic requirements of the individual. Cases have been recorded which markedly improved on increasing the protein intake. MacCann believes in giving one-hundred and fifty grams of protein daily in the diet. He believes the protein should be of high biologic value such as is found in meat, milk and eggs.(65) It has been pointed out by Hoyle that there is no real evidence to support the contention that red meat is to be regarded as more harmful than white meat, fish, eggs, or milk.(67)

Salt restriction should be practised in the treatment of subacute glomerulonephritis. While much edema is probably due to albumin loss, there is evidence that some retention of salt in the tissues still continues.(62)

Careful attention needs to be paid to the non-protein nitrogen of the blood in subacute nephritis. If it starts to rise the proteins need to be restricted at once. Generally with such a rise the edema will start to resolve because the retained products tend to raise the osmotic pressure of the blood plasma. This clearing of the edema is a danger signal announcing that the patient is passing from the nephrotic stage to the stage of renal insufficiency. Treatment,then, must be changed. This treatment will be discussed in detail in the section on chronic glomerulonephritis.(62)

In the subacute phase rest in bed is indicated as this tends to inhibit the development of edema. Patients in this stage are

also especially susceptible to infections of the respiratory tract and should be protected from exposure. What has been said with regard to foci of infection in acute nephritis is also true in this stage.(23)

Fluids are limited from eight-hundred to one-thousand cubic centimeters until the edema disappears. If oliguria persists markedly, a good plan is to limit the fluid intake on a given day to the level of the urinary output of the previous day.(75)

The natural course of chronic nephritis varies so widely (from a few months to fifteen or more years) that it is hard to advocate rules which will apply to all cases. Since the disease is progressive and, in the end, fatal, it is only possible to retard its course and to relieve the symptoms. It is wrong, therefore, to interfere too much with the freedom and activities of the patient. Moderation in all things and avoidance of heavy exertion are to be advised. In the more slowly progressive and early cases it is better for the patient to continue his occupation than to live and introspective and unhappy existance in much reduced circumstances. In more rapid or advanced cases work will be impossible and rest in bed may be essential.(77)

It is agreed there are no drugs which directly influence the disease, and usually none should be ordered. If the patient is constipated mineral oil may be given. For chronic nephritis in the latent or symptomless stage the only other drug which may be necessary for regular administration is iron if anemia is present.

Large doses should be given, such as twenty grains of iron and ammonium citrate thrice daily, or equivalent doses of some of the other proprietary preparations.(77)

Large doses of alkalies have been recommended by some men. Potassium citrate and sodium bicarbonate were given by mouth in doses from one-hundred and eighty up to one-thousand grains daily until the urine was alkaline with a PH of seven to seven and six-tenths. It was claimed albuminuria was not infrequently lessened and even disappeared. However, the risk of overdosage was considerable. Apparently it only amounted to the treatment of an acidosis by the giving of alkalies but it did nothing to relieve the underlying cause.(67) MacAdam has this to say about alkalies from actual treatment of cases of chronic nephritis with them: "The results were disappointing. Moreover, there were decided disadvantages. In many patients large doses of alkalies caused much vomiting, while there was a real danger of alkalosis". (70)

As we are dealing with progressive renal failure the principles on which the diet should be based are quite clear- namely, the protein intake should be restricted to the minimum amount necessary for the replacement of tissue breakdown. This generally requires from three-fourths to one gram per kilogram of body weight daily. It should be emphasized that we should give enough protein to keep the patient in nitrogen balance. The endogenous metabolism

of the tissues will use up this amount of protein anyway, and nothing is gained by reducing the proteins below this level.(71) The organism requires a certain minimum amount of protein which it must have in the diet or this amount will be taken from the the body tissues. However, there is no doubt that careful dieting with this in mind will delay the onset of uremia or actually reduce the amount of nitrogen retention in the blood if it already exists. As there is polyuria and no edema, fluids may be administered liberally, and rigid restriction of the salt intake is neither necessary nor desirable. The ordinary salt required in cooking may be allowed, but extra salt should not be given if the patient has recently passed through an edematous stage of nephritis.(77)

An alkaline ash diet has also been recommended. Beneficial effects were claimed for it. The urine was made and kept alkaline by the giving of a preponderance of foods which metabolized with an alkaline ash. This diet actually seemed to benefit the patients symptomatically. It was better tolerated by them and decidedly a better course to follow than the giving of alkalies. Here question was raised as to whether some of the beneficial effects of the diet were not due to the difference in the nature of the amino-acids supplied because of the different type of protein necessarily found in such a diet when compared with the acid ash diet. This could not be answered. Even though all seventeen of the patients in this series of cases progressively became worse and died of the disease, symptomatically they were made more comfortable for a time on this diet.(63)

The course of chronic nephritis is sometimes interrupted by heart failure. This must always be borne in mind. In one series of cases half of the patients died of cardiac failure. This failure is manifested by the development of dyspnea, venous congestion, hepatic enlargement, and edema of the dependent parts. For this condition rest in bed should be ordered, the fluid in the diet should be restricted to eight-hundred cubic centimeters daily, and ten grains of diuretin are recommended thrice daily. Digitalis may also be of value, especially if auricular fibrillation is present. Morphine can be used to relieve the nocturnal attacks of dyspnea known as cardiac asthma. Letting a pint of blood, or if the patient is anemic, putting a turnicate on an extremity for a few minutes, helps greatly in these attacks. A pericarditis often occurs towards the end of chronic nephritis. It is usually not painful and requires no special treatment.(77)

In cases in which the blood pressure is very high (diastolic one-hundred and twenty, systolic two-hundred and twenty or over) it is common for the patient to complain of periodic disturbances usually ascribed to "billousness". These take the form of severe headache and vomiting, and are often associated with spasm of the retinal arterioles, giving rise to blurring of vision or even blindness. Occasionally unconsciousness and convulsions may occur during such an attack.(77)

These hypertensive crises are sometimes distinguishable from true uremia only by examination of the blood for non-protein nitrogen or urea. During the attacks the patient should be in

bed and the diet consist merely of fruit, water and glucose. An enema may be given, followed by the introduction of three ounces of fifty per cent magnesium sulphate solution into the rectum. Venesection (at least three-fourths of a pint in an adult) may also be performed if there is no severe anemia. Also lumbar puncture is sometimes helpful. Morphine may have to be used to quiet the patient. Chloral hydrate, thirty grains per rectum, may also be prescribed. Chloroform should be employed only as a last resource. After the attack the regular administration of a sedative such as phenobarbital one-half grain three or four times daily may prevent the recurrence of the crisis.(77)

Uremia is the inevitable end result of chronic glomerulonephritis unless some complication takes the patient away before it develops. True uremia is much more insidious in its development than is the hypertensive crisis. General weakness, thirst, dryness of the mouth and skin, drowsiness, loss of appetite, vomiting, and finally coma are its chief manifestations. As soon as the presence of uremia is established by a blood non-protein nitrogen test, if it is possible to obtain such a test, the diet should be restricted to fruit, glucose,and water, or soda water. The fluid intake should be liberal (four pints daily) if not precluded by vomiting. The protein of the diet can be restricted for a few days. However, if this nitrogen retention is a slow process, there is no advantage in limiting the protein to less than the minimal requirement of the individual. Probably the intake should be about forty to sixty grams, otherwise the patient will merely burn his own body protein.

Of late suggestion has been made that only proteins which do not contain any aromatic amino acids be given these patients. This idea is based on Volhard's belief that phenol derivatives in the blood are responsible for the onset of uremia. As yet little is known concerning the practical value of this suggestion.(I3) (72)

Chlorides must be provided to take care of the loss in the urine. Ordinarily five to seven grams of salt added to what is normally present in a salt-poor diet will suffice. In patients who are vomiting it should be supplied parenterally. Fluids should be given liberally as mentioned before (two-thousand cubic centimeters daily) in order to carry out as much waste substance as possible. In the severe cases with acidosis, small amounts of sodium bicarbonate (two to three grams daily) may help. Caution should be exercised in the amount given, however, because of the inability of such patients to handle alkalies well. Alkalosis can be precipitated by an overdosage of sodium bicarbonate. If the symptoms of tetany occur or the blood calcium is very low, small doses of calcium may be given. Attempts to relieve the anemia by iron or liver extract are usually unavailing, unless the anemia has been caused by blood loss or by a deficient diet. Transfusions may give temporary improvement. It is to be remembered, however, that this improvement is only temporary since the factors causing the anemia have not been removed. Repeated transfusions, which reduce the patients financial resources unnecessarily and add only a few days more life, in consideration to the family and everybody concerned, are not to be recommended.(78) Bleeding is said

to be indicated by some men, this to be followed by transfusion. However, it is necessary to point out that any reduction in non-protein nitrogen accomplished in this way is of little value unless the renal insufficiency is due to acute nephritis or some other more or less acute renal failure in which a recovery can be expected. If this is done in chronic nephritis with uremia the non-protein nitrogen of the blood will rise to its previous level again in a few days and little if anything will be gained. Sweating is not to be recommended. It is true that sweating will considerable reduce the non-protein nitrogen of the blood but this treatment so weakens the patient that as much value is lost as is gained. Purging is also of no real value for the same reason and it should not be practised.(72)

CONCLUSIONS

(I) Acute glomerulonephritis is a disease which appears to have a definite relationship to bacterial infections. Most of these infections are situated in the upper respiratory passages and mouth. Hemolytic streptococci are generally the bacteriological agents found causing them.

(2) The pathological lesion, unless recovery takes place, is generally a slowly progressive one which gradually brings about destruction of the functional units, that is nephrons, of the kidney.

(3) Salt retention and protein loss are factors in the production of edema. However, as yet this edema is not well understood and these are probably not the only factors in its production.

(4) As yet there is nothing of value to offer but symptomatic treatment for the disease.

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