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Acute hemorrhagic nephritis

Paul Baker
University of Nebraska Medical Center

UNIVERSITY OF NEBRASKA

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Introduction

It was in 1827 that Richard Bright of Guy's Hospital, London, published the classic "Cases Illustrative of Some of the Appearances Observable on the Examination of Diseases Terminating in Dropsical Effusion". Since that time diseases of the kidneys have been called "Bright's disease". Before this time it was observed that dropsies were associated with failure of the heart or cirrhosis of the liver but Bright noted that one group occurred with an associated condition of the urine which caused it to coagulate on heating. This observation directed his attention to the kidneys which he diligently studied for the following ten years before producing the article mentioned above which appeared in his "Reports of Medical Cases".(30)

More people die of nephritis than of any other diseases except three. It, therefore, behooves the doctor to have as thorough an understanding of this disease as possible. It may occur at almost any age, either sex, under all conditions of life and at any season of the year although, of course, certain conditions and seasons do predispose to the ailment. I refer to the acute hemorrhagic type of nephritis.

In the treatment of any disease it is a great advantage to know the etiology, and hence I shall dwell at length on this phase of the subject.

Classification

In their recent treatise on "The Renal Lesion in Bright's Disease" Addis and Oliver (4) use the following classification.

Degenerative Bright's Disease
- Cryptic
- Pyogenic
- Non-bacterial

Hemorrhagic Bright's Disease
- Initial
- Latent
- Active
- Terminal

Arteriosclerotic Bright's Disease

They found this to be adequate on the whole both as a clinical and a pathological classification. There is however a great deal of over-lapping and this is readily admitted. After Maxwell(36) gives Addis and Oliver's classification he goes on to say that most kidneys can be classified under one of these divisions although it is rare to find a pure degenerative, hemorrhagic, or vascular disease. Usually one lesion will be outstanding with other less marked changes. In hemorrhagic nephritis we find practically always degeneration in the tubular epithelium and sclerosis of the blood vessels in addition to the marked inflammation in the glomeruli. In degenerative Bright's disease, the glomeruli and interstitial tissue show abnormalities. In the arteriosclerotic type glomerular inflammation and epithelial degeneration are present. These associated lesions often play an important part in the course of the disease.

H. A. Christian(13) uses the following clinical classification.

1. Acute nephritis
   Sub-acute nephritis
   (a) With renal edema; nephrosis
   (b) Hemorrhagic nephritis
2. Chronic nephritis
   (a) With renal edema
   (b) Without renal edema
3. Essential vascular hypertension progressing into chronic nephritis
4. Renal arteriosclerosis progressing into chronic nephritis

You will notice that Addis and Oliver use the term "Bright's Disease" while Christian uses "Nephritis". "Bright's Disease" is a general term signifying some variety of kidney pathology but not specifying what type while "Nephritis" would seem to signify an inflammation of some or all of the kidney tissue, as opposed to a "Nephrosis" indicating some degeneration of the kidney substance. I have chosen to head this paper according to Christian's classification (with a slight exception) but shall use "acute hemorrhagic nephritis" interchangeably with Addis' and Oliver's classification of "hemorrhagic Bright's disease".

Etiology

Since the first detailed description of the early lesions of acute nephritis and the recognition of the association of streptococci in the disease by Lohlein in 1907, knowledge concerning its etiology and pathogenesis has made remarkable progress. Volhard and Fahr observed that one-fourth of all the nephritides associated with infection followed tonsillitis and three-fourths of all their collected cases were associated with or followed upper naso-respiratory infections(17). The following case will serve to illustrate the latter factor.

A male medical student, age 25, was subjected to a submucous resection a week after having had a streptococcic sore throat. The sore throat followed his working with a case of erysipelas at the University Hospital over a period of two weeks. (Incidentally, an intern worked with the same case and developed a sore throat with kidney symptoms and findings.)

He complained of a sore throat two days after the sub-mucous resection and two days later developed an acute otitis media of the right ear. This was cleared up and he was dismissed from the hospital on April 24, 1931 but he did not feel well. Four days later he noted that he was unable to void the usual amount of urine. Was advised to go to bed which he did. He developed edema of the legs and some puffiness of the face and entered the hospital on April 30th with a diagnosis of acute nephritis. At the time of admittance he complained of

1. Edema of the face and ankles
2. Malaise
3. Loss of appetite with nausea
4. Voiding small amounts of highly colored urine.

He did not appear ill but said he was tired and that eyes felt peculiar. There was marked edema of the legs and ankles and fullness and tenseness of the skin over the thighs and abdomen. Skin dry and rough. He was partially deaf especially on the right side. There was some nasal obstruction. Heart beat was regular, 60 per minute, no murmurs. Blood pressure 160/90. Abdomen was full but not distended.

Urine examination showed a dark-brown fluid of sp gr 1.022 albumin 4 plus, red blood cells, white blood cells, hyalin, granular and fatty casts. Albumin 20 grams per liter. Hb 74%, red cells 3,810,000, white cells 9,600, with 22% lymphs, 4% monos, 2% young forms, 9% stabs, 61% segmented, 0% basophiles and 2% eosinophiles. The next day there was 7 grams of albumin per liter with a non protein nitrogen of the blood of 78mg per cent, creatinine 2.8 mg per cent. He was given a diet of 1000 calories limited to 20 grams of protein and 1000 cc of fluid

per day. Some edema was noted in the eye grounds.

On May 2nd the albumin was 6 grams per liter, NPN 77mg per cent, blood pressure 140/75, creatinine 3 mg per cent, chlorides 511 mg per cent as NaCl. Sedimentation as follows, 6 mm in 10 min., 12 mm in 17 min., 18 mm in 21 min., 24 mm in 30 min. The uric acid was 5.7 mg per cent.

A urine culture showed gram positive cocci in chains- probably streptococci viridans.

There was a marked reduction of the edema of the body and legs. Urine a little clearer.

On May 12th the calories were increased to 1680 with a total protein of 19 and fluids limited to 1000 cc. B. P. 140/90. Albumin 5 grams per liter, NPN 35 mg per cent, weight 157 lbs. (He lost 15 lbs in wt in the twelve days.) Skin rough and dry and irritated. Calomine liniment applied b.i.d.

On the 18th the protein was increased to 50 grams, salt-free diet, with restricted fluids. Two grams of albumin per liter of urine. Few red cells and white cells but no casts. Weight 145½ lbs.

He was dismissed on June 6th. There was a 2.5grams of albumin per liter in the urine, it was acid, sp gr 1.012, red cells two to three per high power field, white cells, ten to twenty per high power field, granular casts two to three per high power field, cellular and epithelial casts occasionally. Diet 2,750 calories, 70 grams protein. He weighed 146½ lbs. Blood pressure 130/82.

When checked up nearly two years later the urine was negative except for one or two granular casts. The blood pressure was 122/70; weight 165. There were no complaints.

In this case a sore throat preceded an operation on the nose which was followed by an acute nephritis. We might very well suspect that the organisms entered the blood stream in some manner, possibly through the operation wound, and lodged in the kidney. Organisms were isolated from the urine. We can only wonder if the same organism producing the erysipelas caused the sore throat, the otitis media and the nephritis. Perhaps the streptococci are transported to the kidneys where they are engulfed by the cells lining the glomeruli and there set up a diffuse progressive inflammation. However, the fact that the blood and urinary cultures are usually sterile and the inability of pathologists to demonstrate organisms in the glomeruli is sufficient evidence to jeopardize the rationale of this idea. If this were the method by which diffuse inflamatory lesions of the glomeruli were produced one would expect a similar picture in all cases of sub-acute bacterial endocarditis. But the renal lesions commonly found in sub-acute bacterial endocarditis are in the form of a focal glomerular nephritis with only a relatively few glomeruli involved and without any clinical evidence of an acute renal insufficiency.

Sison and Ignacio(53) report on a series of 659 cases of nephritis in Filipinos of which 27 per cent were of the acute type. Among this series acute exanthemata occupy the first place among previous diseases, but in all probability these eruptive fevers had no immediate connection with the causation of nephritis, as the lapse of time between their occurrence and that of nephritis was too long. Undoubtedly other intercurrent infections, such as malaria, influenza dysentery, typhoid fever, rheumatism, etc., contributed a great deal to

damaging the kidneys by the elimination through these organs of the toxic products thereof and those of increased katabolism indident to all febrile conditions. This assumption is strongly supported by the fact that in almost all the cases studied there was a concomitant infection of some kind. The most frequent infections associated with renal disturbances are pneumonia, typhoid fever, malaria, septico-pyemias, tonsillitis, dental caries and scabies according to these Filipinos. The febrile reaction and the increased tissue destruction per se are sufficient to start some organic trouble in the kidneys, but in all probability both together with the infective agents and their toxic products, should be held responsible for the disturbances in the kidneys. They report only eleven cases of acute nephritis due to poisons; six with bichloride of mercury, one with lysol, one with hydrochloric acid, one with alcohol and two with unknown drugs.

Binder(9) states that nephritis complicating measles is comparatively rare but reports a case-that of Beverly M., female, age seven years, who complained March 4, 1931 of cough, fever, sneezing and photophobia.

Past History. Normal baby, full term, second child, breast fed for five months and then put on a formula on account of infantile eczema. She had chickenpox when two years of age and had several attacks of tonsillitis.

Diagnosis-Measles, preeruptive stage, which was confirmed the following day. The course was uneventful until March 11, when the patient complained of pain in the left ear. The examination showed the drum congested. The right ear drum appeared normal. On March 13, both ear drums were bulging and a paracentesis was performed; pus was found. On March 14, ten days after the first visit, the mother noticed that the patient's urine was very dark in color. The child voided freely without any pain. The examination of the urine showed: color, bloody; transparency, turbid; reaction, alkaline; albumin three plus; uncountable leukocytes, many erythrocytes, and granular casts. The urine remained bloody for one week when it became straw color, turbid, ten leucocytes, five erythrocytes, (per high power field)with a one plus albumin. The albumin and casts gradually disappeared, and the cells decreased. On March 27, the twenty-third day of her illness, she developed a severe chill and her temperature steadily rose to over 106 degrees.

The diagnosis of lobar pneumonia was made. On the following day, March 28th, the urine again became bloody, alkaline in reaction, albumin three plus, with an increase in casts and cells.

The pneumonia cleared up promptly and on the thirty-fifth day of her illness the temperature became normal although the ears continued to drain profusely. The urine gradually cleared, and the cellular elements became normal. The temperature remained normal for about six days, when it began to rise again. On April 21, there was a swelling noticed behind the right auricle. On April 22 the patient was admitted to the hospital where she was operated on for mastoid, the fifty-second day of her illness, from which she made an uneventful recovery. In the hospital her urine showed a one plus albumin, thirty leukocytes, no erythrocytes and no casts.

The etiology of measles is rather unsettled. Did the organism that presumably caused the measles also produce the otitis media, the nephritis, the pneumonia and the mastoiditis? I shall attempt to answer this question a little later. This case calls our attention to the fact that the outlook seems to be very much better in children than in adults and in the majority of cases complete resolution of the inflammatory process in the kidney is unattended by any serious after effects.

Addis(1) comments on the etiology of nephritis by saying that a patient has scarlet fever or tonsillitis, and while he is as yet in the stages of convalescence, his urine becomes bloody, his face swollen and he develops a mild hypertension.

Acute rheumatic fever is given by Goldring(22) as one of the acute infections in which nephritis is uncommon, being something like one-half of one per cent. He, however, reports the case of S.M., age 39 years, male. In Feb. 1929 at the age of 37, he had his first attack of rheumatic poly-arthritis and pancarditis. After eleven weeks stay in the hospital he was discharged with no physical or electrocardiological evidense of heart disease. He was next seen seventeen months later (July, 1930) when he was readmitted to the hospital in acute congestive heart failure. The diagnosis made at this time was rheumatic heart disease (inactive), enlarged heart, mitral stenosis, and insufficiency and auricular flutter. He was fully digitalized and the rhythm converted to fibrillation. The rate was controlled with digitalis to an average of about seventy per minute. During the next five weeks he was under observation in the out patient clinic, where in spite of con-

tinued administration of digitalis and a persistent ventricular rate of about seventy he went into progressive congestive failure and was readmitted to Bellevue Hospital Aug. 22, 1930. From the time of admission the temperature ranged between 99 and 101.8 F. On Sept. rth there occurred a serofibrinous pleurisy. On Sept. 11th there occurred pain, redness and swelling of the right ankle and pain in both shoulder joints associated with a rise in temperature. In the next two weeks there appeared successive crops of purpuric spots over the legs and trunk. On Sept. 25th the abrupt appearance of facial edema and marked hematuria indicated the onset of acute diffuse glomerulonephritis. There was no rise in the blood pressure, nor was there elevation of the blood NPN. The weight rapidly increased in the twelve days following the onset from 115 to 133 lbs. On Oct 12th, eighteen days after the onset, the facial edema had entirely disappeared and the patient was greatly improved. The only treatment during this period was water and salt restriction.

Can one assume a direct relationship between the rheumatic infection and the cause of the renal complication? Assuming that a specific strain of streptococci is the causative agent in rheumatic fever, is it reasonable to postulate a causal relationship between the same organism and the complicating nephritis? The possibility of secondary invasion by some other organism or some other strain of streptococcus makes an exact answer to this question impossible.

This record is of clinical interest because of the relative rarity of occurrence of diffuse glomerulonephritis in the course of acute rheumatic fever.

Rosenbluth and Block(52) report three cases of pneumonia followed by acute diffuse glomerular nephritis, the hematuria noted one day after the crisis in one; in the second twelve days after, and in the third, seventeen days. All had had blood cultures positive for pneumococci though first evidence of kidney involvement appeared long after the blood had been found sterile. They report that in some cases, proved by autopsy findings, there is a focal glomerular lesion in lobar pneumonia.

Many years ago E.C. Dickson observed that rabbits and Guinea pigs given one injection of a uranium salt showed a still continuing inflammatory reaction in their scarred and contracted kidneys when they were killed long after they had received that single dose. We know the kidneys he examined were not those which had originally been damaged, for every cell had been many times renewed. We know that no minutest trace of uranium can have been left anywhere within the body. And yet the pathological process was still continuing in the absence of the agent by which it had been initiated and in a medium which had never known uranium. So also in hemorrhagic nephritis it is possible to suppose that the continuance over years and decades of a slow disintegration of the architecture of the kidney might be a result of the structural disorganization produced in the initial stage of the disease. It would not then be necessary to hypothecate the continuing action of any toxin. The scarlatinal endotoxin might act for a day or for an hour and the patient forever afterward be rid of it, and yet its effect on the kidney might not reach its full fruition until that patient died in uremia twenty or thirty years later. During the initial stage it is possible to picture in imagination at least, a laying down of hyaline material between capillaries and cells and a thickening of basal membranes, which would constitute a permanent hindrance to the nutrition and renewal of the cells of the kidney, a crippling alteration in environment, entailing a continuous abnormality and slow failure in the maintenance of the complicated and interdependent parts of the renal elements, which in spite of all concomitant reparative mechanisms, might in the end result in an almost complete destruction of the kidney.

In discussing the etiology of nephritis Alport(5) suggests that there is a toxic factor at the root of all cases causing damage to the glomeruli, followed by tubular degeneration. The same lesion is caused by the toxins of pregnancy, secondary syphilis, and by tonsillitis and certain chemical poisons. He says we fail as a rule to recognize that in those cases in which there is a transition to the subacute and chronic stages of nephritis there is often a secondary or residual focus of infection in the tonsils, antra, sinuses, teeth, or perhaps the intestines, which may account for the failure of the acute renal condition to subside completely. These cases usually begin insidiously and unless the focus of infection is recognized and eradicated at any early stage, a progressive deterioration may occur which sooner or later ends in the death of the patient from pneumococcal infection of the edematous tissue or from renal or cardiovascular failure.

From the point of view of organismal infection of the kidneys, Rosenow's work on the elective localisation of streptococci suggests that oral sepsis may be the focus of infection of bacteria having selective affinity for the urinary tract. Burpus and Meisser(11) have described swellings and areas of hemorrhage and necrosis in the medulla of the kidneys of rabbits after intravenous injections of streptococci from infected teeth or tonsils.

Hartzell and Henrici produced definite suppurative changes in rabbits after innoculation with streptococci, but did not describe anything indicating chronic interstitial nephritis. The presence of chronic inflammatory or degenerative changes,

however, would necessitate a long-continued infection, which is difficult to produce in an animal; this experimental evidence of toxemic kidney is not very conclusive. In the course of injections with streptococci Alport(5) found albumin in the urine of four of the rabbits which developed pyemic joints but recovered under treatment with fixation abscesses.

The effect of a toxin upon the kidneys depends upon its virulence; upon the length of time it continues to be excreted, and thus is able to excite degeneration or inflammatory reaction; and upon the resistance of the kidney tissues to toxic action.

Paterson and Wyllie(49) have shown that 85% of cases of acute hemorrhagic nephritis in children are due to tonsillitis or associated conditions, such as cervical adenitis and otitis media; the causal organism is usually the streptococcus although the staphylococcus and pneumococcus are sometimes found. Acute nephritis, moreover, is very common after scarlet fever and diphtheria, conditions in which infection of the throat is one of the most prominent symptoms.

The association of nephritis and mastoiditis is probably more frequent than the available list would indicate. There are only eight cases reported as such in the past fifteen years(27). If the infection involves the middle ear or the mastoid, then the question of eliminating the focus becomes of paramount importance.

The case that Kinney[1] cites is that of a white boy, age 12 years who on Aug. 22, 1931 was seen with a left acute otitis media or 12 hours duration with no history of antecedent upper respiratory infection or known communicable disease. The past history was negative, the tonsils and adenoids having been removed five years ago. A myringotomy was performed and the patient put to bed. The temperature never came below 38 degrees centigrade. The discharge was copious and on Aug. 27 there was enough evidence to warrant doing a simple mastoidectomy. The streptococcus hemolyticus was isolated from the mastoid. Convalescence was uneventful

and there were no detectable complications.

On Aug. 28, the above patient's younger brother, age nine years, complained of pain in the left ear. The previous history was identical with the older brother's history. The drum ruptured spontaneously five hours after the onset of pain. A myringotomy was performed one hour later to further facilitate drainage. The patient was kept in bed and within four days the temperature curve was flat, all mastoid tenderness had disappeared and except for a decreasing aural discharge there were no symptoms. The patient was kept in bed four more days and a culture of the aural discharge revealed the streptococcus hemolyticus. During this time the child had no signs or symptoms except for the discharge.

On Sept. 5, eight days from the onset, he was allowed to get up. On Sept. 6, he complained of a headache but was not seen by a physician. The next day the temperature was 39 degrees centigrade and the headache was worse. Complete physical examination revealed the following positive points: Blood pressure 138/90; slight puffiness of the eyelids and the face, moderate purulent discharge from the myringotomy wound. The urine was smoky and contained many red blood cells and a moderate number of pus cells. When tested for albumin the tube boiled solid. A pediatrician was called in, who corroborated the above findings. The patient was seen daily by both of us for the next seven days. The temperature averaged between 37.8 and 39 degrees centigrade all the time and except for some accumulation of granulation tissue at the site of the myringotomy, there was no change in the ear condition. The patient became progressively more anemic but there were no other changes.

On Sept. 14, a simple mastoidectomy was done, using only nitrous oxid anesthesia. The mastoid was partially broken down, containing pus under pressure and some granulation tissue in the region of the antrum. Neither the dura of the lateral sinus nor the middle cranial fossa was exposed. Laboratory findings on that day were: hemoglobin 52%; red blood cells 3,800,000; white blood cells, 14,500. The urine was the same as it had been for the previous eight days, except that a few hyaline and granular casts were found. On Sept. 15, a transfusion of 350 cc of blood was given the patient. Culture of the mastoid taken at the operation was lost. The temperature subsided by lysis, the patient's condition improved and he was discharged from the hospital on the eighth day. Laboratory findings on that day were: Hemoglobin 63%; red blood cells 3,870,000; urine, alb plus, and red blood cells plus and no casts.

One week later, the urine was entirely negative and has been on several examinations since. The blood pressure came down to normal, and on the 21st post operative day the wound was completely healed.

This was a case of acute hemorrhagic glomerulonephritis. Was this a case of scarlatina? No less an authority than Jackman states that a scarlet fever kidney never starts before nineteen days from the initial onset. Did the second boy ac-

quire the disease from the first boy? Probably so and stricter precautions should be observed in handling streptococcic ears. Perhaps operation was delayed too long. Evidence of kidney irritation should be an indication for mastoidectomy in a case of mastoiditis.

Bumpus and Meisser(11) point out that the increasing evidence that bacteria are carried by the blood to the kidneys and excreted, as demonstrated by the presence of tubercle bacilli in the urine of patients suffering from pulmonary tuberculosis but with no renal lesions, and the well known fact that typhoid patients excrete typhoid bacilli in their urine, indicates that renal infection may arise from the blood stream.

The fact that the tonsils are not enlarged and that pus is not expressed from them dose not exclude them as possible foci and it is their custom to have tonsillectomies performed in all cases in which a urinary infection may reasonably be believed to be of focal origin.

Bell and Clawson(8) gave a large male rhesus monkey repeated intravenous injections of streptococci over a period of four years producing albuminuria, hematuria, severe toxic symptoms and finally death from uremia.

Whether the bacterial bodies or their soluble toxins were responsible for the renal injury was not determined. The kidneys were at first resistant to injury, but later became highly susceptible. This increased susceptibility of the glomeruli was probably merely a response of injured tissue to repeated irritation. It is not necessary to assume that hypersensitiveness existed. No other organs showed changes at autopsy.

On experimenting with rabbits Bumpus and Meisser(11) found that the infected material from diseased tonsils and teeth, when properly cultured and injected into the animals, produced definite lesions in the kidneys as well as other organs and the bacteria injected were removed in pure culture from the kidney lesions.

A group of men(10) report a small series of rabbits which they injected, for the most part, intradermally with pneumocci in doses ranging from .2cc to .5cc of a moderately heavy one-day old broth culture. Type I produced the most marked effects not only in regard to the local skin reaction and the systemic upset but also in the kidneys. Of fifteen rabbits inoculated with Type I, eleven received what seemed to be a virulent strain, and of these six, or 54.5% showed early changes of nephritis as represented by haemorrhage from the glomeruli into the tubules in all, by the presence of colloid granules in the epithelium of the tubules in three, and by the occlusion of the glomerular capillaries with fibrin thrombi in two.

Eight rabbits were injected with Type II, an avirulent strain. Of these, one showed colloid granules in the convoluted tubules but nothing else.

Eleven were given Type III and all of these showed definite skin reactions at the site of infection. Of these eleven, four or 36.4% showed colloid granules in the tubular epithelium.

In every case pneumococci were present in the capillaries of the kidneys, demonstrating that a general septicemia had occurred. These organisms were always single or in groups of two or three; in no instance were there any clumps which might conceivably be thought to be blocking the capillaries.

Addis says that there must be some other factor in the etiology of nephritis besides virulence of the organism and "constitutional susceptibility". He calls attention to identical twins who both had some upper respiratory infection and one developed nephritis and the other did not and no reason could be found for this difference. Perhaps this factor in some cases is the diet. There is considerable controversy as to the role the diet plays. The question has, however, been investigated by experimental feeding of animals and men.

In 1919 Newburg(41) reported a series of experiments in which renal injury was observed in rabbits to which high protein diets were given. In 1928 a further report(42) was made of experiments in which white rats were given 75% of their diet in the form of proteins, either as liver, or as beef muscle, or as casein. Renal injury was noted in all groups after varying lengths of time. In the group receiving liver, the kidneys at autopsy were enlarged, granular and characterized by both glomerular and tubular lesions and fibrosis in "less than a year" of feeding. In the case of casein the renal injury was least marked, being confined to the tubules, and required the longest time for its production, while the lesions occurring in the group receiving beef muscle were intermediate between the two extremes both in degree and in the rapidity of their production. In a more recent report Newburgh(43) expressed the belief that the difference in results obtained in previous work was due to the nephrotoxic effects of products of nuclear material and not to the proteins per se, since feeding of sodium nucleate produced hematuria. He was

able to produce kidney injury with less than 75% of liver in 80% of animals.

Other workers have reported the production of renal lesions in animals by the feeding of high protein diets. These include Osborne, Mendel, Park and Winternitz(46) and Polvogh, McCollum and Simmonds(50). On the other hand Drummond, Crowden and Hill(18) Jackson and Riggs(25), and Addis, MacKay and MacKay(3) failed to find renal injury in similar experiments. MacLean, Smith and Urquhart(37) were able to produce renal injury in rabbits by means of high protein diets only when green leaves and vegetables were omitted from the diet.

In 1931 Squier and Newburgh reported that albuminuria was increased when large amounts of proteins were given to patients with nephritis, and that red blood corpuscles appeared in the urine of normal men under similar circumstances. On the other hand Addis (1926) counted the formed elements in the urinary sediment of a number of normal adults before and after a single ingestion of one and one-half pounds of meat. No increase was observed.

Two arctic explorers were kept under observation by McClellan and DeBois(38) for one year while subsisting on a protein and fat diet. The protein intake ranged from 100 to 140 grams daily. No evidence of renal damage was discovered by either laboratory or clinical observations.

Pospischill and Weis kept one-half of a series of 2,373 cases of scarlet fever on a diet of milk, while the other one-half received the usual diet containing meat. The incidence of Bright's disease was the same in both groups. The general condition of those patients who received the meat was better.

Jochmann came to similar conclusions in observing a series of one thousand cases of scarlet fever.

Keutmann and McCann(26) made observations on four patients with hemorrhagic Bright's disease, who received at different times both high and low protein diets. In all four patients the acute stages were observed in the hospital. These were cases of diffuse glomerulonephritis, since all exhibited a latent period between the onset of infection and the onset of nephritis, all exhibited impairment of function at some stage, and all had edema. The objective criteria were the erythrocyte count in the urinary sediment indicating the intensity of the process of the disease in the glomeruli and the estimation of renal function by the blood urea clearance tests indicating the degree of impairment of renal function.

The conclusions drawn after the tests on the four patients were (1) Hematuria, as a measure of intensity of glomerular injury, was not increased.

(2) Functional capacity, as measured by blood urea clearance, continued to increase.

(3) Slight increases in proteinuria which occurred in two cases during the high protein diets are believed to be without deleterious significance.

(4) Slight increases in azotemia occurred, which were accentuated by the restrictions of water intake necessary to the making of sediment counts.

(5) Serum protein fluctuated independently of the level of protein intake and of nitrogen balance.

(6) Blood pressure was not increased by the more liberal protein allowance.

(7) General clinical improvement occurred in all cases. Weight increased, anemia improved, and patients returned to their normal state of strength and vitality.

Cramer(15) found that on a diet excluding magnesium fed to rats albumin was found in considerable amounts in the urine after four or five weeks. The kidneys showed degenerative lesions on this diet with increased connective tissue around the degenerated tubulee but with no evidence of an inflammatory reaction. These experiments show the possibility of producing experimentally degenerative changes in the kidney by dietetic measures which do not involve the introduction or formation of toxic substances, but which appear to result from a mineral imbalance, having a specific effect on the glomeruli and tubules.

One hypothesis is that diffuse glomerular nephritis is caused by a toxin produced by streptococci or other bacteria in a focus of infection distant from the kidney. One would conclude from most of the literature that the writers believe that the renal lesions are produced by continuous or recurring blood stream toxins formed in a focus and injuring the glomerular cells in the process of elimination. The ~~the~~ work of Trask and Blake(55) of Yale University Medical School suggests strongly that there is one other important factor necessary for the development of renal lesions. They clearly showed that a toxic substance can be isolated from the urine of patients suffering with scarlet fever, a disease in which the prototype of diffuse glomerular nephritis is manifested. This urinary substance is neutralized by human serum that blanches the rash of scarlet fever, presumably scarlet anti-toxin, but

not by human serum that fails to blanch the rash. Now these cases of scarlet fever were not complicated by nephritis. In other words there was no clinical evidence of renal injury in these cases in which a toxin of streptococcus scarletinae was present in the urine. This is conclusive evidence that in scarlet fever some other factor in addition to urinary toxin must be present to facilitate development of acute diffuse glomerular nephritis. Furthermore, it has long been observed that the occurrence of scarletinal glomerular nephritis does not seem to have any direct relation to the severity of the disease, very mild cases as well as severe ones being subject to it.

Schick and von Pirquet suggested, many years ago, that the acute nephritis of scarlet fever might be interpreted as an allergic manifestation of this disease(23). If the heightened skin reactions to the filtrate of haemolytic streptococci can be interpreted as allergic reactions, then perhaps many patients, suffering from acute nephritis, are quite highly allergic to some constitutent of hemolytic streptococci or to substances elaborated by these organisms. Though the idea that the diffuse glomerular lesions are produced by the direct action of a pure toxin cannot be dismissed, it seems much more probable that the reaction in the kidney may be allergic in nature, and dependent upon a sensitization of the kidney cells to the hemolytic streptococci or the products of their growth. O'Hare and Kirk(45) skin tested seven hemorrhagic nephritis cases with streptococci and every one of them indicated a sensitivity to these organisms. Five were sensitive to hemolytic streptococci and two to the viridans

strain. By contrast, skin tests done on other types of nephritis thus far indicate that the majority are non-sensitive.

Long and Finner(29) attribute a coagulation necrosis of the glomeruli and tubules found in one kidney of a tuberculous pig four days after perfusion with tuberculin protein to anaphylactic inflammation. Longcope(31) has reported an experimental nephritis in sensitized animals by repeated proteid intoxication. This, however, was produced by anaphylactic shock and not as a local reaction of the renal tissue.

Arthus(24) injected rabbits subcutaneously with a foreign protein every six days and found that local toxicity of the protein steadily increased. The onset of this phenomenon is not dependent upon the number of injections entirely, as there are individual variations and a great many injections may be necessary. The reaction is not the result of the amount of protein injected. The preliminary sensitization could be made by any parenteral route. The severity of the local reaction differs with the location of the tissue injected. Anaphylactic inflammation is characterized by its rapid course and the intensity of the reaction.

Hepler and Simonds(24) used commercial horse serum and a 2% solution of crystaline egg albumin and injected the skin and kidneys of rabbits. They found that the inflammatory reaction in the sensitized animal was marked whereas in the control rabbits there was only hemorrhage due to mechanical injury. The anaphylactic inflammation produced in the kidneys of these animals differed from other forms of inflammation (a) In the rate of progress. (b)In the relatively slight edema in the inflammatory areas in these kidneys as compared with

similar areas in the subcutaneous tissues. (c)In the extent of the necrosis which is primarily of the coagulation type.

Probably the cause of the necrosis was the direct toxic effect of the antigen on the sensitized tissues. This is suggested by the fact that the more highly specialized and differentiated tubular epithelium of the cortex appeared to be more susceptible to injury than the less highly specialized epithelium of the collecting tubules of the pyramids. The antigen remaining concentrated at the site of the injection caused the necrosis and inflammation to be localized and more intense.

Ernstene and Robb(19) report a familial epidemic of diffuse glomerular nephritis in which six of ten children were effected. This is of particular interest because the cases clearly illustrate certain feature of the pathogenesis of the disease.

In the second week of Jan. 1928, T.G., aged 8, an American born schoolboy of Greek parentage, became ill with fever, mild sore throat, coryza, headache and severe general malaise. These symptoms lasted six days. During the following seven weeks, there developed in three sisters and two brothers, successively, a similar acute infection of the upper respiratory tract, which lasted from three to seven days. In each individual hematuria and edema appeared from seven to twelve days after the onset of the illness. None of the patients presented evidence of scarlatina, and three had had that disease several years earlier. None had had a previous attack of acute nephritis. There was no family history of allergic conditions such as hay fever, asthma, food sensitivity or urticaria. The patients were treated at home for from one to six weeks and then successively entered the hospital because of persistence of symptoms and signs of nephritis.

Cultures from the throat showed many colonies of streptococcus viridans in all patients. Three of the subjects also showed streptococcus hemolyticus and three of Bacillus influenzae. Cultures of the urine remained sterile in all.

The similarity of the initial acute infection in all the patients indicates that the infections probably were caused by the same type of micro organism. The development of the illness successively in various members of the family suggests, further,

that the causative organism had been transferred from one individual to another. In these patients absolute proof as to the identity of the causative micro-organism could not be obtained, but the isolation of large numbers of streptococci of the viridans type from the throat cultures of all six subjects is of considerable significance. The presence of hemolytic streptococci in one-half of the cases suggests that earlier bacteriologic studies might have shown this organism in all subjects.

The hypothesis that acute diffuse glomerular nephritis results from the development of an allergic state during the process of immunization to the primary infection is widely held at present(32) and justly so according to Lukens(34). The symptoms and signs of the acute nephritis appear from seven to twelve days after the onset of the acute infection of the upper respiratory tract. The length of this interval may be considered additional clinical evidence of the role of allergy in the pathogenesis of acute hemorrhagic nephritis.

The rare occurrence of familial epidemics of acute diffuse glomerular nephritis may be due to the fact that a familial tendency to this type of allergy is uncommon or that many individuals possessing the allergic tendency escape infections which would become the source of the nephritis-producing allergen.

Lukens and Longcope(33) describe a form of glomerulitis which could be produced in rabbits by a single injection of killed suspensions of hemolytic streptococci in the left renal artery. In the normal rabbit this procedure rarely produced a glomerulitis, but in the sensitized rabbit a more or less extensive, and sometimes a diffuse glomerulitis occurred with considerable frequency. It was suggested that the occurrence of the glomerulitis was probably related to the

sensitization of the animal to the hemolytic streptococcus. It was observed that the appearance of glomerular lesions was usually associated with the retention of the bacterial bodies in the glomerular loops, and it seemed possible that the local circulation in the kidney might have some influence om this factor. A series of experiments was therefore devised to determine whether glomerular nephritis could be produced in the normal rabbit by altering the circulation in the kidney. In none of these experiments(34) did the various measures that were employed seem to influence the retention of bacterial bodies in the glomerular capillaries and none of the animals showed a glomerulitis.

It was next desired to know what effect would result from repeated injections of killed haemolytic streptococci into the renal artery of the same kidney of a normal rabbit. These experiments demonstrated that repeated injection at intervals of seven days of killed hemolytic streptococci into the renal artery of rabbits result in an inflammatory process affecting both the glomeruli and the interstitial tissue, and lead, moreover, to changes in the tubules with cast formation. An then, the important thing--that these observations, furthermore, indicate that the inflammatory process does NOT start with the FIRST injection and progress after subsequent injections; but suggests, instead, that the first two injections cause insignificant or minimal changes, and that the extensive and acute alterations occur suddenly after the third injection. Under the conditions of the experiment, one cannot be sure that this is actually what happens, for to exclude the possibility of a gradual pro-

gressive lesion, it would be necessary to examine the same kidney after each injection.

Since the histological changes in the kidney are almost exactly the same as those previously obtained in the sensitized or infected rabbits, it seems probable that somewhat similar alterations in the reactivity of the kidney were induced locally by these repeated intravascular injections. Under these circumstances the inflammatory reaction of the kidney, found after the third injection of killed hemolytic streptococci into the renal artery, might be considered as analogous to the Arthus phenomenon(44). It is known that reactions similar to the Arthus phenomenon may be obtained experimentally in the organs of the body.

Hepler and Simonds(24) describe areas of necrosis and hemorrhage in the kidneys of rabbits which followed the direct injection of horse serum and egg albumen into the kidneys of animals which had previously received 1 cc. of horse serum or 2 cc. of albumen at five to six day intervals subcutaneously.

Long and Finner(29) produced inflammatory or tuberculin-like reactions in the kidneys of tuberculous pigs by perfusing tuberculin into the renal artery.

Anderson(6) reports a case of tuberculous meningitis which entered the Belfast Infirmary Feb. 4, 1931. Tubercle bacilli were found in the spinal fluid on Feb. 6th. On Feb. 22nd the patient contracted a mild attack of influenza with headache and general pains. Progress after this was very slow. He left the hospital March 18th.

The patient was readmitted on April 4th with an acute attack of nephritis having felt quite well until a few days previously, when he developed a severe pain in the back, with swelling of the feet and legs, and frequency of micturition with pain. There was pus and albumin in the urine, but repeated examination failed to find organisms. The albumin persisted, and in the middle of May the patient had an acute exacerbation, with blood two plus in the urine, but still no organisms could be discovered. He left the hospital June 17th and has been able to undertake heavy manual labor.

The sputum and urine were examined repeatedly for tubercle bacilli, with negative results. The radiogram of the chest showed no evidence of any tuberculous involvement of the lungs, but a general enlargement of the chest shadows; the radiogram of the abdomen showed a calcified mass of glands in the right side opposite the fifth lumbar vertebra. The Wasserman was neg.

Fox, Mantel and Rabens(21) emphasize the toxic etiology of nephritis by citing a case where absorption of toxins from an acute obstruction of the small intestine resulted in an acute toxic nephritis as manifested by the sudden increase in blood pressure, albuminuria and casts. Experimental bismuth intoxication and abdominal trauma are given as causes. A French writer also calls attention to a nephritis of intestinal origin. Another writer cites the possibility of a specific virus as being the cause of primary nephritis. There are also cases reported following parotitis and prostatic abscess.

Summary of the Etiology

There are three main theoretical considerations of the mechanism involved in the pathogenesis of acute hemorrhagic nephritis. These are (1)the transportation of streptococci to the kidneys where they are engulfed by the cells lining the glomeruli and there set up a progressive inflammation; (2) a toxin produced by streptococci or other bacteria in a focus of infection distant from the kidney, and injurying the glomerular cells during the process of elimination; and (3) the nephritis is an allergic reaction or anaphylaxis, if you please, as a result of the kidney being rendered hypersensitive to streptococci or their products.

A number of men have produced nephritis in animals by injecting them with streptococci and have removed the organisms from the kidney lesions, demonstrating that a general septicemia does occur. The organisms do not block the capillaries mechanically but must produce the lesions by liberating toxins which destroy the kidney tissue. This toxic action is shown also by the injection of KILLED streptococci with resulting kidney lesions. The same lesions are caused by the toxins of pregnancy, secondary syphilis, and by tonsillitis and certain chemical poisons such as bichloride of mercury and lysol. The effects of the toxin depends upon its virulence; upon the length of time it continues to be excreted; and upon the resistance of the kidney tissues to toxic action.

However, it has also been pretty definitely shown that nephritic patients give skin reactions to toxic filtrates from the hemolytic streptococci. Animal experiments and clinical observations support the idea that acute hemorrhagic nephritis develops in those whose kidney cells have been rendered hypersensitive to the hemolytic streptococci. Following scarlet fever there is an interval of several days before the acute nephritis develops. This is added evidence that the complication is an allergic phenomenon.

The factor of diet in the production of nephritis is unsettled. There is evidence on both sides of the question. Animal experimentation on the whole seems to show that a high protein diet causes renal damage, while observations on patients go to show that this is not true but on the other hand is really beneficial.

Symptoms, Course and Pathology

Acute hemorrhagic nephritis is marked regularly by hematuria, proteinuria, and edema, while diminution of renal function, hypertension, plasma protein deficit, and some anemia are frequent. The patient may first notice that his urine is dark or bloody and that he voids a very small amount. The first symptom may be malaise, headache, anorexia, nausea or even backache. Edema usually occurs promptly and is most noticeable about the eyes, then the ankles. The patient may notice that he cannot draw up his belt as far as usual or simply that his abdomen is enlarging. His skin feels tight and his eyes "queer". The skin is hot, dry, and rough and the tongue coated.

The acute stage may have one of four outcomes. (1)The patient may completely recover, without any detectable sign of the disease remaining. (2)He may improve and become free from subjective symptoms of the disease, but retain some albuminuria, hematuria, or diminution in renal function, the disease becoming latent. (3)The disease may progress into the active chronic form, almost always with subsequent more or less gradual progress to the terminal stage. (4)The disease may hasten in a few weeks directly from the acute to the terminal stage, and in a few months terminate in uremia.

In Van Slyke's series of cases the duration of the acute stage, in the cases which recovered or improved to the latent stage, varied from four to fifteen months. Noticeable improvement began within four months, in all cases that were not destined to pass into the chronic or terminal stages.

In the cases which recovered most slowly the last subjective symptom to disappear was the tendency to edema formation. The last clinical sign to disappear was usually the proteinuria, which frequently persisted for months after the patients were subjectively well, and after hematuria could no longer be detected by ordinary microscopic examination. Sometimes, however, microscopic hematuria has been noted as the most persistent sign.

After the acute stage has lasted for a period of two to four months, unless the patient is fated to pass into the chronic or terminal condition, he begins to improve, and makes either a complete recovery, or a partial one to the latent condition, in which he is subjectively well, but in which more or less albuminuria or slight hematuria, or a subnormal blood urea clearance, indicates that renal conditions are not quite restored to normal. Usually the blood pressure is now normal, but in an occasional case some hypertension may remain.

When the condition becomes chronic there is diminished urea excreting power and signs of active progress, but the blood urea clearance is still above 20% of normal.

In some cases the subject remains ill, malnourished and usually edematous. Hematuria continues, but sometimes at so diminished an intensity that the red cells are detectable only microscopically by Addis' special method of examining by quantitative count the sediment of urine passed during the last twelve hours of a twenty-four hour dry diet. The renal function as measured by the blood urea clearance, maintains a steadily downward progress.

The active chronic stage is usually accompanied by marked proteinuria, low plasma albumin and total protein content, tendency to edema formation, and by the occurrence from degenerated tubules, of epithelial cells and casts in the urine. Hypertension is absent in some cases of chronic hemorrhagic nephritis. Microscopic hematuria appears to be the most consistent finding.

With the progress of the disease the picture eventually changes from that outlined above for the active chronic stage and assumes that of the terminal. Renal function becomes stabilized at a lower level, and no longer shows occasional upward fluctuations. The edema, albuminuria, epthelial casts and cells in urinary sediment, low plasma albumin content, may continue undiminished to the uremic end, but they usually diminish and often disappear.

With the rise of plasma albumin which frequently occurs during progress into the terminal stage, the tendency to edema diminishes. At such a time the patient is likely to feel subjectively improved. This period constitutes the preuremic interval of the terminal stage and may last as long as two years.

Urea Excreting Power

Maintenance of normal renal function during the first months of the acute stage does not justify a good or a bad prognosis. Nor can we attach prognostic significance to the degree of functional impairment shown during the first two months.

The essential for a good prognosis is that within four months after the acute onset the clearance, if it has fallen,

shall have begun a consistent climb back to a normal level. The functional recovery is not always complete although subjectively it is. Considering that an occasional healthy person may show a clearance as low as 70% of the average, however, 50 to60% indicates a satisfactory function if maintained. The explanation is that some of the glomerular damage of the acute stage has become permanent, but a large proportion of the glomeruli have recovered and remain intact for considerable, perhaps indefinite, periods.

In all of Van Slyke's cases in which marked fall of blood urea clearance occurred during the initial months, and no definite tendency to rise followed within four months after onset, progress downwards to the active chronic or terminal stage followed.

In the chronic active period of hemorrhagic nephritis the blood urea clearance is gradually lowered until death from uremia follows in three months to a year or two.

In the terminal stage, with renal function less than 20% normal exitus is by uremia in three months to two years unless hastened by cardiac failure or other intercurrent cause.

Hematuria

Every case of acute nephritis exhibits some hematuria. The degree of initial hematuria appears to have no relation to the prognosis. Nor does the period of persistence of hematuria appear to have any close relationship to the outcome.

Because of the fact that during improvement to the latent condition hematuria and hypertension frequently disappear before albuminuria, plasma protein deficit, and the tendency

to edema show much improvement, one can easily make the error of diagnosing such a case as nephrosis, unless the history of initial hematuria is known.

In the active chronic stage of hemorrhagic nephritis again the degree of hematuria appears to bear no relation to the severity or rate of progress of the disease. This is also true of the terminal stages although in this stage the hematuria is usually microscopic.

Blood Pressure

There is practically always some elevation of blood pressure at the onset of acute hemorrhagic nephritis. The duration in the favorable cases is four to six weeks. One cannot ascribe any prognostic value to the initial blood pressure level observed during the first weeks of acute hemorrhagic nephritis.

According to the result of Branch and Linder (1926) and Van Slyke, permanent marked hypertension developing during chronic hemorrhagic nephritis usually indicates the addition of an arteriosclerotic element tothe pathology of the disease. Uremia does not appear to come on much, if any, more rapidly in cases with hypertension than in those without. A marked fall in blood pressure is not uncommon in the last weeks or days of terminal nephritis in cases that have previously had hypertension. Such a fall is presumably a sign of heart failure.

The definite significance that does attach to hypertension is that it marks the type of case in which death may occur from circulatory failure before renal failure has reached

a lethal degree, or in which death may occur from a combination of cardiac and renal failure.

Plasma Protein Content

Unlike the urea excreting power and degree of hematuria, plasma protein content appears to be of decided prognostic significance during the acute stage of hemolytic nephritis. Acute hemorrhagic cases that maintain plasma albumin above 2.2 per cent, or total protein above 5.5, have a better prognosis than those that do not.

A low plasma albumin content, usually below the 2.5 per cent level at which albumin deficit begins to produce edema, is the rule in the active chronic stage of hemorrhagic nephritis.

As the active chronic stage passes into the terminal there is a marked tendency for the plasma protein to rise towards normal.

Proteinuria

In acute hemorrhagic nephritis the degree of initial proteinuria appears to have no prognostic significance.

The duration of the proteinuria in the cases of Van Slyke that recovered was from two weeks to five months. In all the acute cases which improved to the latent stage proteinuria persisted, but showed a marked diminution from the initial output. In about one case out of five the urinary protein sinks to a trace during the final period in the terminal stage.

Edema

Edema

An exception to the relationship of plasma protein concentration and edema occurs in the initial period of acute hemorrhagic nephritis, where temporary edema occurs even in cases that do not show sufficient deficit of albumin in the plasma to produce of itself edema. It is evident that the initial edema of acute nephritis is attributable in part, and in some cases entirely, to some factor of this frequently toxic period other than lack of plasma albumin. Such initial edema unaccompanied by plasma albumin deficit appears to be temporary, disappearing within two months of the onset of the disease.

In all Van Slyke's latent cases edema was absent, and plasma proteins were above the critical levels. In the chronic active cases the correspondence between edematous tendency and plasma albumin deficit was practically uniform.

It appears that in the terminal stage of edema, when it occurs, may be due either to cardiac failure or to plasma protein deficit.

Anemia

In the acute stage there is a considerable degree of correlation between the anemia and the degree of fall in renal function indicated by the blood urea clearance. In prognosis the temporary anemia of the acute stage is of no more significance than the temporary fall in blood urea clearance and the absence of anemia is likewise no guarantee of a mild course or probable outcome.

In the latent stage anemia is absent or slight while in

the active chronic stage there may or may not be anemia. It is nearly always present in the terminal stage. While the presence of anemia signifies a grave prognosis, the maintenance of nearly normal hemoglobin does not gainsay the immediate onset of uremia.

The following case of acute, hemorrhagic nephritis progressing directly into the terminal stage and exitus, presented by Van Slyke(56) will serve to emphasize the pathological findings in the kidney at autopsy.

Case 23. Hosp. No. 6112. F.S., Male, 44 years.
The patient two years before admission had been told that his urine contained no albumin and that his blood pressure was normal. Four months prior to coming to the hospital, he had contracted a severe cold which had been followed by arthritis. There had been no gross hematuria or edema.
On admission the patient was in an uremic condition. There was severe anemia. The hemoglobin was 8.8 volumes per cent O_2 capacity. There was no edema. The heart was not enlarged. The urine contained a quantity of albumin, red blood cells, white blood cells and casts. Many of the casts were of the broad renal failure type. The blood urea nitrogen was 117 mgm. per cent, the creatinine 9.9 mgm per cent. The phthalein output was but 2% in two hours.
During the two months that the patient was under observation, the blood urea nitrogen remained between 91 and 117 mgm per cent. The creatinine stayed at 9 mgm per cent. The phthalein excretion was reduced during the second month to a trace in two hours. The hemoglobin was constant at 8 volumes per cent, O_2 capacity. The excretion of albumin, red blood cells and casts continued. Slight edema appeared a few days before death. There was a slight elevation of the systolic blood pressure level during the last month, -the diastolic level remained normal. The patient died in uremic coma.
Autopsy. Autopsy No. 283/1927. Three hours after death.
Death by bronchopneumonia. Fresh serous fibrinous pleurisy. Serous pericarditis. Ascites. Old healed endocarditis. Neither the right kidney, nor its ureter and arteries could be found. The left kidney was very large. The capsule stripped with difficulty. The kidney was doughy in consistency. Its surface was smooth and occasionally slightly granulated. It was yellowish white in color showing red blood dots. The cortex was much enlarged showing a picture similar to that of the surface. The cortex was well marked off from the medulla.
Microscopic examination.
All glomeruli are severely diseased. Their tufts are en-

tirely clotted by hyaline masses. Nearly all glomeruli are empty of blood and show partially increased numbers of nuclei. Occasionally one sees necrosis of the loops. Nearly all glomeruli are adherent to the capsules to a large extent. In the capsular spaces one finds some coagulated protein and erythrocytes in places. The covering cells of the glomeruli as well as the parietal epithelial cells are much increased in number and show frequently typical crescents. The capsules are thickened and cannot be sharply differentiated from the surrounding tissue.

The tubules are frequently dilated and contain some coagulated protein, casts, some erythrocytes and polymorphonuclear leucocytes. Their epithelial cells are much desquamated. Some are flattened. Others are swollen and occasionally show hyalin droplet degeneration. The interstitial tissue is thickened in some instances and contains cellular infiltrations. The arterioli are relatively well preserved. The larger arteries show only initial hyperplasia.

Addis and Oliver(4) state that everyone from Virchow's time admits that the lesions in Bright's disease are both mixed in nature and diffuse in distribution. The irritating substances reaching the kidney by the arterioles are thrown into the capillary bed of the glomeruli and produce a violent reaction. The capillaries are dilated, leucocytes are extruded, protein leakage occurs and even thrombosis and necrosis may result. Those elements that, from their anatomical structure and nature, may respond by degenerative changes, do so. Fatty degeneration or even necrosis is found in the endothelial cells of the tuft and the rudimentary epithelium of the capsular space. Bowman's space is filled with exudate so that crescents form in the extracapillary type of lesion or if the process is more or less contained within the tuft, the intracapillary form of glomerulitis result. In the meantime the toxic substance has reached the tubular epithelium. Since the blood has passed through the glomerular capillary bed previously and has produced there the violent reaction we

have described, it is possible that its toxic properties have been reduced before it reaches the epithelium. It may be, on the other hand, that these poisonous substances have been excreted through the glomeruli or reach the epithelial cells only by absorption from the lumen of the tubule. At any rate there occurs as a response to them the only morphological reaction of which the epithelium is capable, that is, degeneration. Different tissues, glomeruli, and tubules, have responded in their own way to the irritant and there is no need to think of any interrelation or dependency of one process upon the other.

The variation that is found in hemorrhagic nephritis in the degree of these epithelial reactions is not surprising when one considers the great variations which may occur in the amount of "toxin" or its concentration in the blood stream as it reaches the kidney or as these factors may change as it is distributed throughout the kidney. Both the inflammatory and degenerative lesions as they develop may alter these factors so that again one would expect irregularity of occurrence and distribution in the epithelial lesions. On the other hand since the glomeruli receive the blood first and directly from the arterial supply a comparative constancy in reaction would be expected in them.

The interstitial tissue of the kidney as well is affected by the bacterial poisons, and its response again is determined by its anatomic peculiarity. Inflammation is the striking lesion, though here too degeneration or even necrosis may occur in its constituent cells. But these changes are always

insignificant as compared to the hyperemia, edema, and the exudation of leucocytes which characterize the early stages of the imflammatory process. The tubules may be actually separated by the accumulations which occur between them and the whole kidney may become tense and swollen within its capsule. To these exudative inflammatory phenomena are soon added the productive changes of the inflammatory process, which consist of proliferation of fibroblasts, the development of collagen fibrils, and the accumulation of "round cells" such as lymphocytes and plasma cells.

There may be a gradual recession of the activity of the process, the disease passing into the latent stage. After such a period of latency the processes may pass back again into an active stage and this recession and exacerbation of the activity of the lesions may be repeated several times.

If the tissue destruction is of the diffuse type it may conclude the history. If the lesions are patchily distributed and there is considerable renal parenchyma preserved the disease passes into the terminal stage with kidney failure.

So the processes continue until a point is reached when the kidney is no longer able to perform its excretory function and fails. Not only is this a failure of nitrogenous secretion, but the failing organ can no longer free itself of detritus in a normal manner and broad renal failure casts form in the ducts of Bellini and appear in the urine. The kidney, perhaps only a tenth its original volume, is no longer sufficient and so death results from uremia.

In the eleven cases of hemorrhagic nephritis in Van

Slyke's series of fifty that came to autopsy practically all of the glomeruli were destroyed. This finding taken with the fact that the blood urea clearance was reduced to the neighborhood of 5% of normal or lower in these terminal cases, indicates the probability that in hemorrhagic nephritis the fall in blood urea clearance is proportional to the glomerular destruction.

Five of the eleven cases were clinically classified, because of marked hypertension and cardiac enlragement, as arterio-sclerotic in addition to the primary hemorrhagic disease. All of these cases showed, in addition to the glomerular destruction, marked arteriolar changes at autopsy.

Two cases which went from the acute stage directly into the terminal, in contrast to the other nine, did not show contracted kidneys, although glomerular destruction was practically complete. The kidneys were of the large white type and doughy in consistency. In each kidney the surface was relatively smooth with very fine, slight granulations. The cortex was a little enlarged and in color similar to the surface. Fine radiate brownish stripes were visible in it. The cortex was fairly well marked off from the brown red medulla.

The striking finding in the kidneys following hemorrhagic nephritis is the destruction of the glomeruli. The kidney is at first soft, swollen, large, and white. After the process has continued for some time and the scar tissue has contracted,, the kidney is small, contracted and hard.

Treatment

In the treatment of acute hemorrhagic nephritis there are three chief manifestations of the disease to be combated(28). First, actual or threatened uremia; second, edema; third, hypertension. The actual treatment of acute nephritis reduces itself largely to the treatment of symptoms. There are no measures known to medical science that will directly influence the pathological changes in the kidneys; and all that can be done is to insure that the patient is placed under the most satisfactory conditions for recovery of the damaged renal cells.

The view is generally accepted that a diet low in protein is indicated in the early stages especially in cases showing a retention of nitrogenous waste products in the blood. When this is a marked feature, a diet in which the necessary calories are furnishes in the form of carbohydrates often does well. On the other hand, the mistake should not be made of unduly limiting the protein intake for long periods, in all instances in which there is marked albuminuria. For certain cases, often complicated by persistent edema, the amount of protein actually passed in the urine may be so great as to constitute a serious loss, and in such cases it is worse than useless to restrict protein intake(20). Very often we relieve the edema by greatly increasing the protein part of the diet(7); the action of which is dependent to some extent on the diuretic action of urea formed as the result of increased protein metabolism. Ervin and Kimmel(20) state that their experience convinces them that the nephritic does better, that there is

less secondary anemia, asthenia is much less marked, the conviction of invalidism is not as noticeable to the patient, friends and relatives, and the patient enjoys life much more, when he is permitted a liberal intake of protein in accordance with his own food desires.

In bad cases with severe general disturbance the amount and nature of the food must often be determined by the state of the patient's stomach. Sugar is exceedingly beneficial in the form of 50% glucose in orange juice; if vomiting, give by vein, 25% glucose in saline, 200 cc. with twenty units of insulin(54). Insulin (because it is a hydrator) brings back to the protein particles of the blood their other constituents-electricity, salts, sugar, amino-acids and fat. Consequently insulin is an antidote against any substance which causes or predisposed to inflammation, be it of bacterial or of chemical origin. In glomerular nephritis, insulin makes the blood plasma more liquid and the vessel walls more elastic, producing vascular dilatation. In all renal conditions with high blood pressure, in uremia and acidosis, insulin is the remedy of choice.

When more food can be taken, the diet may be made up of milk sparingly with cereals and, after a few days, bread, butter, and cooked rice with milk may be added. In severe cases with marked edema it is a very good plan to keep the patient on a starvation diet for a day or two; this lowers the general metabolism of the body and provides functional rest for the damaged kidneys. Gradually as the edema disappears and symptoms become less urgent, more and more carbo-

hydrates may be added to the diet. In general it can be said(39) that if the adult with nephritis takes a quart of milk daily, two eggs and one large serving of meat, his need for protein will be covered and no harm will be done his kidneys.

The fluid intake depends to a great extent on the amount of edema present, whether increasing or diminishing, the amount of urine secreted, the presence or absence of vomiting and other factors. In spite of restricted fluids and salt free diet, edema may prove very troublesome and persistent; in such cases fluid must be aspirated sometimes when there is excessive fluid in the abdomen or chest. The aspiration may have to be repeated several times. One of the best means of dealing with edema is the free use of purgatives, especially large doses of magnesium sulphate in concentrated solutions, if the stomach will tolerate them.

——Diuretics seem to be of no value in acute nephritis. In this condition the renal cells are poisoned, and it is difficult to imagine how any substance could stimulate into activity these temporary inactive tissues. There success is almost entirely confined to cases of nephrosis or cardiac edema. In acute nephritis, a condition accompanied by convulsions, and in certain respects somewhat similar to the uremia of chronic nephritis is occasionally seen. This so-called "uremia", with convulsions appears to occur only when extensive edema is present, and is probably dependent on a local edema of the brain. These convulsions are sometimes preceded by a definite increase in the edema and a progressive rise in blood pressure with severe headache. As already indi-

cated they are not usually of serious import and are best treated by large doses of sedatives and cathartics or by venesection. If headache is severe, and blood pressure is rising, potassium bromide, 15 grains with chloral hydrate ten grains, should be given every four hours until the blood pressure begins to fall. At the same time free purgation should be induced by giving magnesium or sodium sulphate one or two ounces. Morphine in doses up to ¼ grain may also be used. With the actual onset of convulsions, 30 grains of potassium bromide with 30 grains of chloral hydrate dissolved in two or three ounces of water should be given by rectum. If the convulsions are not very frequent this sedative may be given by mouth. When the convulsions are very frequent and severe a small amount of chloroform or ether may be necessary. By far the best treatment is the removal of ten or fifteen ounces of blood from the vein; lumbar puncture has frequently been employed and with fair results, but the procedure is usually unnecessary. In the pre-convulsive stage it sometimes precipitates the onset of convulsions, so that it should be performed only, if at all, after convulsions come on.

When the heart begins to show signs of failure from increased blood pressure and general toxic conditions, digitalis may be given with some benefit. If the stomach permits 20 minims may be given every four hours until signs of digitalization appear. If there is much cardiac distress, with right heart embarrassment, venesection is useful. The complete suppression of urine, which is sometimes seen, is merely an

indication of the severity of the condition and cannot be materially influenced by any therapeutic measure. Muscular twitchings suggestive of tetany often complicates a case, especially one in which large amounts of alkalis have been administered during a course of fever or other acute infections, and usually suggest a calcium deficiency and is often cleared up by the administration of one grain of calcium chloride in 40 cc. distilled water, injected into the gluteal muscles every hour for four or five doses.

In the treatment of all cases of nephritis, the greatest care should be taken to ascertain the presence of septic foci and to remove these conditions when possible. Dr. Ed Clay Mitchell(35) of Memphis reports the case of a male, seven years of age, who developed edema two weeks after scarlet fever. The urine was dark red in color, containing many red blood cells. He was only passing two or three ounces daily. The sinuses were found to be acutely involved. The tonsils had been previously removed. The sinuses were drained under local anesthesia. After several washings the amount of urine increased and the character of the urine became normal. The child made an uneventful recovery. Particularly in the subacute case with much edema does removal of focal sepsis appear to give the best results.

The best results are obtained when the tonsillar abscess or other infection has been eradicated at a very early stage. Blood colored urine, seen before the removal of tonsils, is often clear as soon as 48 hours after removal. The tonsils are by far the most common harbor of hemolytic streptococci.

Occasionally the organism is in a sinus or a discharging ear. Then a satisfactory result can only be secured by the eradication of the infectious process in the sinus or ear.

Vaccine treatment is only worth trying in cases in which there is definitely no focus of infection in the mouth or sinuses or in which the removal of a focus of infection is an impossibility.

There may be hesitation in the removal of foci of infection for fear of temporarily producing an exacerbation of the symptoms. Page and Alving(47) state that tonsillectomy, adenoidectomy and tooth extraction have usually had no effect on kidney function. In three out of thirty-one cases, however, renal function was depressed in the days immediately after operation. Renal blood cells and casts in the urine were frequently increased for some days after operation. Such increase usually occurred without any fall in renal function. When the general hygiene of a renal patient demands such an operation it is not necessary to refuse it, unless the renal disease is in the terminal stage, or the general condition of the patient is unfavorable.

It is probable that focal sepsis plays a definite part in the etiology of the nephritis associated with pregnancy, even if it is not the actual cause of the condition; thus it should be sought for in the early stages of pregnancy with albuminuria, and what is more important, eradicated if found.

Summary

There has been a difference of opinion between the clinician and the pathologist as to the best classification of "Bright's Disease". Perhaps the nearest agreement as to classification is reached in the one presented by Addis and Oliver where three types are distinguished as (1) Degenerative Bright's Disease, (2) Hemorrhagic Bright's Disease, and (3) Arteriosclerotic Bright's Disease.

The etiology of acute hemorrhagic nephritis is discussed under four headings, (1)streptococcic, (2)toxic, (3)allergic, and (4)dietary. The streptococcic etiology has been proven by fulfilling Koch's postulates, and by clearing up the condition by removal of streptococcic foci of infection. The toxic etiology is represented by nephritis occurring following intestinal obstruction, during pregnancy and after the injection of killed streptococci. The time interval between scarlet fever and complicating nephritis suggests the allergic etiology. The factor of diet in causing nephritis is unsettled.

The disease may clear up completely, become actively chronic, assume a latent condition or become terminal. Improvement must begin within four months from time of onset or the case is destined to pass into the chronic or terminal stages.

Prognosis is measured by the ability of the kidneys to excrete urea, by the proteinuria, plasma albumin, tendency to edema formation, and by the occurrence from degenerated tubules, of epithelial cells and casts in the urine, by the hypertension and the microscopic hematuria.

Acute hemorrhagic cases that maintain plasma albumin above 2.2%, or total protein above 5.5% have a better prognosis than those that do not. So, unlike the urea excreting power and degree of hematuria, plasma protein content appears to be of decided prognostic significance. While the presence of anemia signifies a grave prognosis, the maintenance of nearly normal hemoglobin does not gainsay the immediate onset of uremia.

The kidney of the acute hemorrhagic nephritic is large, smooth, yellowish-white in color and shows red blood dots. The glomeruli are severely damaged, many being replaced by clotted hyaline masses. Glomerular circulation is at a standstill and occasionally necrosis of the loops is seen. The tubules also become dilated and the epithelial cells are desquamated, swollen and degenerated, and appear in the urine as casts. The interstitial cells became swollen and there may be leucocytic infiltration apparent.

The treatment of acute hemorrhagic nephritis is, in the main, symptomatic. We still do not know how to rest the kidney. We limit protein intake in cases showing a retention of nitrogenous waste products in the blood. A diet high in carbohydrates is advocated, with insulin to make the blood plasma more liquid, to reduce the blood pressure and combat acidosis. Edema is combated with saline purgation, limitation of fluid intake, elimination of salt from the diet, tapping, diuretics, heart stimulation, and often times by greatly increasing the protein part of the diet. Headache and convulsions are perhaps due to brain edema and are relieved by spinal drainage, hypertonic intravenous glucose solutions,

venesection, purgation and sedatives. Anesthesia may become necessary.

In the treatment of all cases of nephritis, the greatest care should be taken to ascertain the presence of septic foci and to remove these conditions when possible at the earliest opportunity.

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March 1933. # Paul Baker