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Etiology of glomerular nephritis

Ben E. Ewing
University of Nebraska Medical Center

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OF
GLOMERULAR NEPHRITIS

By

Ben E. Ewing

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Introduction

In making a study of the "Etiology of Glomerular Nephritis, one of the principal difficulties has been the nomenclature. This is easily understood when it is remembered that in this condition exist a number of symptoms and states which are among the least understood in medicine--edema for instance, high blood pressure, and arteriosclerosis.

Through-out this discussion, the term glomerular nephritis refers to that condition in which there are inflamatory changes in the glomeruli. The evidences of inflamation are: swelling and proliferation of the capillary endothelium, accumlation of blood and leucocytes in the glomerular capillaries and formation of intra-capillary fibres. In addition to the intra-capillary changes, there maybe an exudate in fibrin, leucocytes and red cells. The result of these various inflamatory reactions is narrowing or closure of the glomerular capillaries, and it is this process which brings about the subsequent structural and functional alterations in the kidney. Tubular

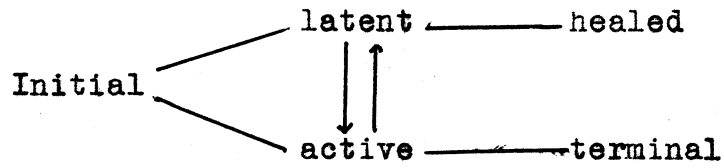
injury is of secondary importance.

It was in 1827 that Richard Bright (12) first described the signs and symptoms of persons afflicted with renal disease. Some years later, he wrote: "It is, indeed, an humiliating confession, that although much attention has been directed to this disease for nearly ten years yet little or nothing has been done towards devising a method of permanent relief when the disease has been confirmed; and no fixed plan has been laid down as affording a tolerable certainty of cure in the more recent cases." One hundred years later, Cecil (12) writes that we must amplify this apology of Bright with the equally humiliating confession that we, today, cannot cure the disease; furthermore, its etiology and the mechanism of its progression or of spontaneous healing remain obscure. Until the causative factor or factors are revealed, only emperical treatment at the best can be expected. Satisfactory statistical study of its incidence, course, and outcome can be determined only after the etiology has been established. Although there are numerous quite satisfactory classifications, the ideal one, which naturally is an etiological one, cannot yet be established. Only after proper classification can adequate,

rationalistic, scientific therapy be administered to the patient. It is with this in mind that an attempt is made in this paper to correlate some of the important factors in the etiology of glomerular nephritis.

Clinical Course

A brief description of the clinical course of glomerular nephritis is of paramount importance in aiding one to more clearly and accurately understand the factors envolved in its etiology. In brief, the clinical course is varied. During its progress, the dominant features of the illness may change in such a remarkable manner that from superficial examination, the different stages may seem to bear few resemblances one to another. The complete picture must usually be pieced together from information obtained from observation made over comparatively short periods of the patients illness. The following graph of the disease is taken from Addis and Oliver (1).



It is the initial, or acute phases, and the terminal stages that are most familiar. Less is known about

the intermediate stages of the disease. The initial or acute stage maybe replaced by an insidious on-set, almost free from symptoms or signs, except for the appearance of albumin, casts and blood in the urine. This form has been designated by many as a focal glomerular nephritis. It is seen most frequently during the course of an acute infection. In all probability, the cases of benign hemorrhagic nephritis, described by some authors, would fall into this category. The desirability, however, of regarding these cases of hemorrhagic Bright's disease (classification of Addis and Oliver (6)) with insidious and comparatively benign on-set as distinct from the more serious type of disease, is dubious; for Addis (1) and others have shown that, in some instances, the symptomless initial phase may progress to a latent phase and the latter to the typical form of glomerular nephritis. In occassional instances, the amounts of albumin, of red blood cells and of casts, which are found in the urine of these patients with an insidious on-set, but without other symptoms or signs, are in all respects the same as those found in patients with an acute on-set attended by the marked hypertension, anasarca, nausea and vomiting characteristics of the

on-set of severe acute hemorrhagic nephritis. Indeed, there is less and less tendency to attempt to distinguish on clinical grounds alone, a focal form of glomerular nephritis.

Following the acute, or initial stage, the disease may progress, as is well known, in a variety of ways. Rapid and complete recovery may ensue, or the patient may become symptomless and the renal functions normal, but for weeks or months there may be albumin, casts or red blood cells in the urine. This latent phase may end in recover, change later to an active stage (also called nephrotic stage) or it may progress without this variation in symptoms, after months or years, to the terminal phase. In many instances, the initial stage runs imperceptibly into the active, latent or terminal stages. After weeks or months the active stage may be replaced by a latent phase, resulting occasionally in recovery, but more often terminating fatally. A few patients die in the acute attack; others progress rapidly from the initial to the active stage and die with a few weeks or months with massive edema, hypertension and hematuria.

Infection and Glomerular Nephritis

Since the days of Richard Bright (1), the relation between nephritis and certain infectious diseases has been recognized, for in his original descriptions of the disease he states: "A child, or an adult, is affected with scarlatina or some other acute disease; or has indulged in the intemperate use of ardent spitits for a series of months or years: he is exposed to some casual cause of 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 happens, 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 albumen: his pulse is full and hard, his skin dry, he has often headaches, and sometimes a sense of weight or pain across the loins."

Pancoast[35] in 1882 in an effort to explain the cause of Bright's disease, suggested that the causes be classified as primary and secondary, the latter

recognized as the exciting cause. The primary was an ennervation of the organic nervous systems. The secondary being the one which makes manifest the primary cause. Scarlet fever, acute infections, mineral poisons, alcohol, pregnancy and protracted and low forms of fever were all given as secondary causes. He attributed the chronic froms to the same things but most especially fast living, mental strain, anxiety and heriditheriditty.

The idea that bacteria might be concerned in the production of nephritis may be said to date back almost as far as bacteriology itself. Ophulus (37) states that it was Ernst (37), who worked under Klebs (37) in Zurich, who was one of the first to recognize that true nephritis, being a genuine inflamation was probably due to infectious agent. Although Kanneberg (35) in 188- had called attention to the fact that pathogenic bacteria might be encountered in the urine of acute infectious diseases especially when they were associated with nephritis and that tonsillitis is a very common cause.

Councilman (34) in 1897 after a careful study of twenty-eight cases, reports that in eighteen of these bacterial infection was found either in the kidney or

other parts of the body. Fourteen of these were evidently streptococcus, and in eleven of these there was present endocarditis and general septecimia.

Little (34) in 1907 was able to appreciate the frequency with which acute infections, namely scarlet fever and tonsillitis, preceeded the on-set of nephritis; but of greater importance to him was the environmental conditions which he believed out-weighed acute infections as a cause of nephritis. He was able to show that the Chinese are approximately a vegetarian people who do not use alcohol as a beverage. Nephritis exists in these people but not so commonly as people in the United States. In a group of wild animals examined, mostly mice, rats, birds of different varieties, and fish, there was no evidence of nephritis. With domestic animals, there is evidence of nephritis, but much less frequently than in man. From this, he hypothesized that certain diseases, including nephritis are closely related to that complicated artificial environment which we call civilization. The analogy between nephritis and environment has probably been over emphasized in that there are for example too many other factors than the vegetarian diet of the Chinese which may stand in an etiological

relation to kidney disease as clothing, lack of bathing, tea drinking, opium smoking, etc. Also, pathogens for man may be as harmless in other animals and for this reason it is difficult to compare them with man except in carefully controlled experiments.

Acute glomerular nephritis is a manifestation of an infection in one part or another of the body. While such factors as cold may play an important part as predisposing causes, recent investigations have shown more and more clearly that the primary and essential cause is infection.

Dr. Ophulus (24), 1915, states that from his studies it appears that the cases of the acute condition were caused by a septic infection, usually the streptocaccus, and the death of the patient is due to the over-whelming infection, the nephritis playing a minor role. In the sub-acute type, he believes the etiology is very evident in a comparatively recent history of tonsillitis, rheumatism and other forms of streptococcus infection with or without endocarditis. The etiology of the more chronic cases is difficult to detect, but in his opinion a careful study of the clinical

record usually reveals a very definite history of repeated attacks of tonsillitis, rheumatism or other septic troubles. In some of these cases, it is possible to recover the old septic process at necropsy. He emphatically stated that septic and mostly streptococcus infections were the basis for glomerular nephritis. Also, he contends that it is the continuance of this infection in more or less hidden foci which keeps the process in the kidney going.

Two years later, Ophulus (91) published results of more work which confirmed his original idea that glomerular nephritis was a well-defined disease of the kidneys caused by general sepsis arising from infected focus; and often made progressive by the persistance of such focus. In his cases; tonsillitis was found to be the most frequent preceding condition and he reports that many of the chronic cases seemed to be caused by a peculiar form of chronic suppurative tonsillitis due to a diplo-streptococcus.

Loncope (90) states that since the early work of Loehlein, it has been recognized that acute glomerular nephritis may not only follow scarlatina,

but may also follow or be associated with several other varieties of acute infection, In his series of forty cases, he has shown that the on-set of acute or sub-acute glomerular nephritis was preceded or accompanied in 85% of the cases by an acute infection, such as: tonsillitis, sinusitis, bronchopneumonia or scarlatina; of this 85%, cultures showed 68.7% to be streptococcus of the beta type and streptococcus of the alpha type in 12.2%. Ten cases apparently recovered from the acute nephritis; in nine of these the infection and infecting organism had disappeared. In 10 of the 12 cases, which progressed to the chronic stage or terminated fatally, the infection or infecting organism had persisted. No evidence from this study would indicate that the streptococcus had caused the nephritis by actual invasion of the glomeruli as the blood and urine cultures were all negative. In fact, in two of the above cases studied by Loncope (20), the infectious focus could not be demonstrated even at necropsy. Never the less, as maintained by Bell and Hortzell (7) these "idio pathic" cases are in all ways so nearly identical with those occurring in connection with

manifest infectious focus that their origin in infection seems certain; their studies were made from 32 cases. The associated infections made either at autopsy or from clinical findings show acute endocarditis to be the most frequent cause, being present in 37% of the cases. There were 6 cases of bacteremia, 5 cases of purulent pleuritis and 3 cases each of peritonitis, erysepilas and septic sore throat.

Loncope (29) and his workers in 1929, again demonstrated the definite relation of infection, particularly streptococcus to glomerular nephritis. In a series of 48 cases the bacteriology at the on-set of the nephritis was reported as follows: 24 cases of tonsillitis--16 of which were caused by beta hemolytic streptococcus. 4 cases of scarlatina--2 of which were caused by beta hemolytic streptococcus. It is apparent from this series that tonsillitis and sinusitis are the greatest offenders, as they represent 37 of the 48 cases.

Winken Werder (27) made a careful analysis of a series of 78 cases of glomerular nephritis belonging to Dr. W. T. Loncope (30)--among the various forms of infection noted at the on-set those of the

upper respiratory tract comprised 67.6% of the total number; of these tonsillitis was by far the most frequent, representing 41% of the cases--there were only two cases of scarlet fever. They were able to oberve pneumonia in four cases.

Fifty-two of these cases were apparently the result of hemolytic streptococcus. Twelve were the result of alpha streptococcus. In 11 cases there were no demonstrable organism. The relation of the streptococcus to the progress of nephritis was shown by the fact that the number of cases in which occurred diminished markedly during recovery but persisted durying the progressive stage. Ninety percent of these cases were positive in the active stage. In 68% of these the organisms were no longer present when the patient passed into the latent phase or became well. In the case of progressive nephritis 73% gave positive cultures during the initial stage.

In a study of 77 of these cases with relation to the character of the infection observed at the on-set of nephritis revealed that the cases of glomerular nephritis preceeded by acute infections manifested by local and constitutional reactions

almost always ended in recovery or entered the latent phase. Those associated with chronic infection at the on-set almost always became progressive. The average prodromal period between infection and on-set of nephritis was 11 days.

The seasonal variation consisted with the months during which respiratory infections were most frequent. Exacerbations of nephritis occurred most frequently in the latent and progressive stage of the disease, and in most instances followed infection of the upper respiratory tract. Surgical removal of foci of infection failed to influence the out-come of disease.

Hill (22) in his studies emphasized the fact that in nephritis must be looked upon some-what differently from nephritis in adults; the wear and tear of the patient's past life need not be considered. The condition of the circulatory system etc. are of less importance here, and in general the etiology is not so confusing. Hill (22) states that in spite of the fact that many men fail to stress the importance of tonsillitis in the etiology of glomerular nephritis, it has been his experience that this condition is by far the most frequent cause of nephritis in children. Of 51 cases

he studied of glomerular nephritis, there were 14 directly attributable to tonsillitis and 15 which were probably associated with tonsillitis. Scarlet fever, otitis media and impetigo were apparently each the cause of 4 cases. Two cases were traced to tonsillectomy before the acute infection had subsided. Carious teeth were definite factors in two cases.

The difficulty in determining the etiology of glomerular nephritis is again emphasized by Blackfan who writes: "In the adult especially the etiology and pathology an often clouded by a variety of chemical and bacteriological agents which acting persistently and repeatedly may effect the renal structures in different ways and by the element of time which permits the development of a multiplicity of anatomical changes." In his series of 24 cases, tonsillitis in 14, otitis media in 3, acute upper respiratory in 2 and laryngitis in 1 case preceded the on-set of renal symptoms. Alpha hemolytic streptococcus was recovered from the rhinopharynx in 14 of 24 patients. Throat cultures were not made of the remaining 10.

Cecil (4) states that from his observations

that disease of the upper respiratory tract, be it tonsillitis, pharyngitis, sinusitis, the common cold, "grippe", peritonsillar abscess, scarlet fever, rheumatic fever, etc., is usually associciated with streptococcal invasion when it is followed by acute glomerular nephritis.

Bell (7) in 1937 states that there is usually a history of preceding infection, and that by far the most common are those of the upper respiratory tract, i.e. sore throat, tonsillitis, scarlet fever etc.. In most instances the antecedent infection produces a lesion on the mucous membrane which allows entrance of the streptococcus into the tissue.

The following table taken from Fishberg (17) and modified by Cecil (12) shows rather wide variations in the pathological conditions thought to be responsible for the on-set of acute nephritis. This lack of consistency results probably from the different type of service in the hospitals from which the statistics were gathered and probably to a greater extent from the variations in criteria used to establish the diagnosis. Nevertheless the preponderance of infection of the respiratory tract is obvious.

Primary condition.

	per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent
Angina.....	28	44	29	24	29	50	28	19	17
Peritonsillar abscess...	..	..	..	..	..	..	9	9	6
Scarlet fever.....	0	25	8	27	3	8	4	4	9
Pneumonia.....	11	10	4	9	4		5	5	0
								1	0.7
						8		2	2
Bronchitis.....	0	0	0	0	0		0	1	1
Otitis and mastoiditis..	0	5	8		0		2	8	4
Influenza.....	2	1	0		5	0	1		
				11					
Rhinitis.....	1	*	0		4	0		16	8
Cold (exposure).....	0	0	2		2	0			
Sinusitis.....	0	4	0	0	0	27	31		
Diptheria.....	0	4	0	0	0	0		0	0.6
Rheumatic fever.....	0	0	0	3	0	0		4	1.6
Purpura.....	0	0	4	3	0	0	1	1	0
Impetigo and pyoderma.....	17	0	8	0	20	0	0		
Infection of wounds and adenitis.....	0	0	0	10	1	6	0	16	8
Pregnancy.....	0	0	0	6	2	0	0		
Cellulitis of arm.....	..	..	..	..	..	..	..	0	0.6
Erysipelas.....	0	1	0	1	0	0	1	0	0.6
Staphylococcus infections	..	..	..	..	..	..	..	3	4
Tonsillectomy.....	0	0	4	0	0	0	0		
Osteomyelitis.....	0	1	0	0	0	0	0		
Measles (during epidemic).....	15	0	0	0	0	0	0	1	4
Tuberculosis.....	0	0	0	4	1	0	0		
Unknown.....	26	3	31	3	27	..	15	10	32
Mumps.....	0	0	0	0	0	0	1	1	0
Typhoid.....	0	0	0	0	0	0	2		
Total cases.....									

SCARLET FEVER: It is rather generally accepted that nephritis frequently follows scarletfever, and often it is said that the most important complication is that of acute glomerular nephritis- often referred to as post-scarlatinal nephritis. It almost invariably occurs between the eleventh and the seventh week after the onset of the disease--most commonly about the twentieth day. The incidence of glomerular nephritis following scarlet fevervaries considerably.Mc Crae[18] found well marked urinary changes after the febrile period in ten percent of 1034 cases of scarlet fever; approximately 5% showed sufficiently marked abnormalities to warrdnt the diagnosis of nephritis and in about 2% there were extra renal manifestations of nephritis. Quote from Fishberg[19]:"Rolly observed post scarlatinal glomerular nephritis in 7% of 1400 cases. Steiner and Johannessen studied an epidemic of scarlet fever in which over 70% of the cases were complicated by nephritis. On the other hand, Caiger found nephritis in only 3.3%of 2078 cases of scarlet fever. Friedlander encountered post scarlatinal nepritis in 43 of 229 necropsies on scarlet fever patients. Scarlet fever is much less apt to be

followed by glomerular nephritis in adults than in children. Thus, Caiger found the incidence of nephritis in scarlet fever to be 3.6% in children under 15 years of age; but only about .75% in patients over that age." Cecil [12] states that it is found in about 1o% of all patients with scarlet fever and in about 50% of those with membranous angina.

Post scarlatinal glomerular nephritis is thus one of the group of manifestations of scarlet fever that generally appears after the disease is seemingly over. Glomerular nephritis may follow mild cases of scarlet fever as well as severe ones. Some times the preceding infection is so mild as to be over-looked.

TONSILLITIS: The preceding table illustrates the importance of infections of the lymphoid tissue of the throat, particullary tonsillitis, in the etiology of glomerular nephritis. Many of the cases of unascertainable etiology were probably preceded by mild upper respiratory infectios which did not dire ct the attention. Glomerular nephritis is most often seen a few days to a week after the height of the infection, although it may appear any time.

Often it follows extremely mild as well as severe cases. In the presence of chronically infected tonsils it is difficult to decide ~~whether~~ the part they may play in the genesis of the renal condition. Fishberg states that the close, but as yet totally unexplained relation of tonsillar infection to glomerular nephritis, is further illustrated by; (1) acute glomerular nephritis may occur after tonsillectomy. Hill (22) mentions 2 cases and Fishberg (23) one. (2) when infected tonsils are removed in a patient with subsiding glomerular nephritis, there is often an exacerbation of the hematuria and less often the other symptoms.

SUB ACUTE BACTERIAL ENDOCARDITIS: Loncope (30) divides acute glomerular nephritis into two separate forms the focal and the different type - in the focal whether it is embolic or simple the kidney is not affected as a whole - and in most instances the urinary picture alone reflects the injury inflicted on the isolated glomeruli. He states: "The focal glomerular nephritis as far as is known is always an accompaniment of an acute infection and the embolic form occurs almost characteristically in bacterial endocarditis."

Baehr and Lande (4) in a series of necropsies of twenty-seven cases of bacterial endocarditis found →

the diffuse glomerular nephritis in nine cases. Two were of the acute kind and seven of the chronic type. In their studies they were careful to differentiate a true inflamatory process from multiple glomerular embolization which is always present.

Libman (27) in his original description ofthe clinical picture of the bacterial free stage of sub acute acterial endocarditis states that this stage is often completely dominated by the manifestations of glomerular nephritis.

Cecil (12) s ates that bacterial end ocarditis and other septic states are not infrequently associated with embolic and local inflamatory lesions in the kidney and occasionally typical glomerular nephritis is su per imposed on these lesions; the latter is most frequently seen in casesof infection with streptococcus viridans.

PNEUMONIA: In the rare cases in which glomerc lar re phritis complicates penumonia, it may occur either at the height or after the crisis; in spiet of the few cases of Nephritis complicating pneumonia, febrile albuminuria is quite common. In most cases reported, in view of the description of cases in which edema is general absent, only a minority represent true glomerular nephritis the others are focal forms.

"Fishberg (13) states that West (19) did not find a true Nephritis in one hundred cases of pneumonia. Although Blackman and his workers have produced changes experimentally, with an autolysate of pneumococcus type I which are quite typical of glomericular nephritis. Blackman (9) and Rake one year later showed that apparently the occurance of glomerular nephritis is limited to infants suffering from chronic pneumonal infections such as empyema, organizing pneumonia or pericarditis.

TUBERCULOSIS: Nephritis by many authors is said to be a common complication of pulminary phthisis; more likely a diagnosis of nephritis is made on albuminuria or edema or both which in a tuberculous patient may result from other sources. Long and Finner, in their experiments were able to produce glomerular lesions by injecting tuberculin into renal artery of swine with milde bovine tuberculous. Fishberg (16) found nine cases of glomerular nephritis in 100 patients with early but active pulmonary cases of tuberculous.

RHEUMATIC FEVER: This ondition and glomerular rephritis have often been linked together and easily detectable albuminuria and cylinduria running roughly parallel with the pyrexia are fairly common. Goldring (17) and Wyckoff have shown urinary findings rather typical of glomerular nephritis during the febrile stage.

They

They have reported a marked increase in red blood cells and casts, detected by the Addis counts, and persisting for eight to ten weeks. Bahr (17) and Sacks report five cases of glomerular nephritis due to actue verruous endocarditis diagnosis of the heart condition was not possible at necropsy, however, as the typical aschoff bodies could not be demonstrated. Fishberg (17) reports two cases of acute glomerular nephritis in autopsy findings of patients dying during the febrile stage. Friffith and Mitchell (21) state that nphritis occasionally complicates the rheumatic state but less frequenlly in children than adults.

WAR NEPHRITIS: During the World War there were a great many cases of acute glomerular nephritis reported The disease was almost entirely confined to those men in trenches. Maclean (24) and others thought probably thiswas due to a virus, however, streptococcus, spirochetes and many other organisms were blamed by various men. Apparently it was an infectious disease, a predisposition to which may have been created by cold and other hardships of the trenches. Dunn and McKnee (12) have shown conclusively that it was a true nephritis.

PREGNANCY: Dr. Peters (41) in a recent article states that the relation between pregnancy and nephritis still is not clear. It is his belief that pressure on

the splanchnic vascular system in pregnancy may be an active factor in the elevation of arterial pressure by interferring with one of the most important vaso regulatory mechanisims. The course of chronic glomerular nephritis is apt to be very unfavorably affected by pregnancy. In many cases this is the first evidence of preexisting kidney disease. The symptoms of glomerular nephritis appear early in pregnancy. Those of the true kidney of pregnancy (low kidney reserve) appear late; termination of pregnancy may not stop progress of glomerular nephritis even though signs and symptoms do improve. Pregnancy, per se, is rarely if ever an important factor in etiology of glomerular nephritis. Cases seenin pregnancy are more probably an exacerbation of a quiescent chronic glomerular nephritis.

OTHER INFECTIONS: Evidences of renal disease may be seen in almost all acute infections. In most instances this is merely a focal form of nephritis. In those cases where true glomerular nephritis is present, it is probable that secondary infection with streptococcus isresponsible for the disease.

PREDISPOSING FACTORS:

AGE: Because of improtant role of scarlet fever and acute upper respiratory infections, glomerular nephritis is most common in childhood. Next to childhood

adolescents are next. Rarely are the aged affected with the acute stages. There have been reports of the condition developing in the utero or during first few months of life. Chronic forms occur at all ages but is predominantly disease of the earlier periods of life.

The following table is taken from Fishberg (17):

Age at death	Number of cases
1-10	7
11-20	11
21-30	15
31-40	9
41-50	9
51-60	2
61-70	1
Over 70	0

SEX: Most authors find very little difference in the sex. Dickinson (14) found that of 105 cases in children, 58 were in boys and 47 in girls, while of 54 cases in adults 33 were males.

Cecil (11) found a preponderance of the disease among males in a ration of approximately 2-1.

FAMILY PREDISPOSITION: Some instances of family predisposition have been reported. However, in most of the cases, this appears to be a matter of coinsidence. Those cases of Bright's disease which do seem to run in families are usually found to be essential hypertention rather than true glomerular nephritis.

TRAUMA: It is unlikely that trauma could result in a true inflamatory process in the glomeruli; however, it is known the kidney is very sensitive to mechanical insults. Albuminuria often follows direct blows or palpation. The cases reported giving trauma as an etiologic role were not clinically glomerular nephritis in most cases. In those cases in which a true inflamotory process existed in the glomeruli coincidence was probably the biggest factor.

EXPOSURE TO COLD: The role of exposure to cold is thought to be a factor of rather great significance, especially by the early writers, in relation to the onset of acute glomerular nephritis. Since the role of infection is better understood and more careful bacterological and immunological studies have been

made, the role of cold appears to be less important. Nedzel (17) in a series of experiments showed that the kidney responds to heat and cold applied to the skin, just as the skin itself does. These vaso motor reactions are accompanied by increased permeability and permeation of endothelial walls of the capillary blood vessles;presence of pathogenic bacteria in blood gives them an opportunity to invade the kidney. Vaso constriction of the kidney produced by exposure of the body surfaces to cold causes; (1) increased permeability and permeation of bacteria circulating in the blood through the blood vessel into the kidney tissue and, (2) absorption of bacteria which penetrated into the kidney tissue would also be decreased and would give them time to gain stronghold. During upper respiratory infections the streptococcus which are so often present may be absorbed into the circulation. Due to the changes in the kidney and organisms present nephritis results. It is known organisims are excreted in urine; therefore in order to set up inflamation there must be sufficient changes in blood vessels of kidney to allow bacteria to permeate them. In view of these experiments it seems probable that exposure to cold may in some cases be a definite factor in the etiology of glomerular

nephritis.

EXPERIMENTAL WORK

CHEMICALS AND TOXINS: A vast amount of experimental work has been done since it is only in recent years that any particular attempt has been made to differentiate glomerular nephritis from nephritis in general there is considerate difficulty in evaluating some of the work.

In 1910 Pearce (39) calls attention to the statement of Sollman (39) who said, "All metals cause nephritis. Other nephrotoxin substances are aloin, coal tar products, alcohol anesthetics, oxalates, cantharidin, essential oils, snake venom, ricin, obrin, bacterial toxins, hemolytic poisons and nephrotoxic immune serums. These were tubular poisons. Glomerular poisons he listed as arsenic, cantharidin, snake venom and uranium nitrate.

Pearce (40) interpreted the variety of symptoms of nephritis produced by these poisons as being due to the different points of elimination, but he pointed out that the distinction between tubular, vascular, or glomerular was not so distinct as commonly thought.

Lyon (21) in 1904 produced acute lesions of the kidney by using cantharidin, corrosive sublimate, and diphtheria toxin all of which were considered glomerular poisons. His results were disappointing and it is doubtful if he was dealing with a true glomerular nephritis.

Ophulus (35) in studying chronic glomerular nephritis attempted to produce lesions typical of this condition by the administration of lead salts, by mouth, in increased doses over a long period of time. In his experiments pigs and dogs were used. Because of the resulting anemia the experimental animals were hard to keep alive. The pigs showed no important changes. In some of the dogs there were marked interstitial changes, yet no albuminuria or cylinduria; not any of them showed a true glomerular nephritis.

Uranium Nitrate was thought to be a good glomerular poison. With this in mind, Dickson (14) attempted to produce chronic glomerular changes by the use of this poison. He was able to produce definite attacks, rather typical of glomerular nephritis, followed by recovery of the animal. Pathological studies showed definite damage but no true inflamatory changes in the glomeruli.

Christian and O'Hare (29) have probably done the most extensive work on uranium nitrate poisoning. Anatomically they were able to observe the following types of changes in rabbits.

Hyaline droplets in the endothelium of the tuft, fibrin thrombi in capillaries, hemmorrhage into the tuft with slow coagulation, dilatation of Bowman's space with a granular material, and proliferation of endothelium of the tift, and less often of the capsular epithelium. Although these changes are rather suggestive of glomerular nephritis, it is probable that they were dealing with a degenerative Process, or at the best, a focal form ofnephritis.

Diphtheria toxin is another poison with which considerable work has been done. Baily (30) injected rabbits with diphtheria toxin alone or in combination with pituitary extract. Although there were no proliferative changes present he interpreted the changes as closely resembling those found in the acute or sub acute glomerular nephritis in man.

Frothingham (31) three years earlier and Faber (11) in the same year were unable to observe changes characteristic of human glomerular nephritis, although both injected rabbits with sub lethal doses of

diphtheria toxin.

Leiter (34) some years later probably reported the most conclusive evidence concerning poisons and toxins. He was especially interested in producing the chronic type. He devised the following experiments.

I. Twenty-one rabbits were given intravenous injection every two or three days of a streptococcus viridans, isolated from a removed tonsil. All animals lost from one sixth to 1/3 body weight but showed no other symptoms. In none of the kidneys was there any suggestion of acute or sub acute glomerular nephritis.

II. Forty-nine rabbits were injected with both diphtheria toxin and streptococcus virdins. Diphtheria toxin was given subcutaneously. The susceptibility and reaction of the animals to the diphtheria toxin varied extremely. In general, there were seen extreme hyperemia and dilatation of the glomerular capillaries, endothelial degeneration, hyalin thrombosis in some of the loops and, what was very conspicious but present in only sixteen of forty-nine animals, globular glomerular hemorrhages into the tuft itself giving so called blood cysts. These changes were ascribed to the toxin. The streptococcus injected

seemed to have no effect at all on the damaged glomeruli.

III. A series of twenty-six animals received from 1-8 injections of rattle snake venom. A total of from ten to sixty-six miligrams of poison was given subcutaneously. The usual bacterial suspension, described above in experiment I, was injected introvenously every two or three days. In two animals the venom caused immediate death and in every case there was extensive muscle necrosis even at a great distance from the site of injection. The majority of animals died between five to ten days. One lived as long as forty days. As regards the kidneys, beyond hyperemia and degeneration of glomerular endothelium, with a granular precipitate in some instances in Bowman's ( ) capsule, there were no significant glomerular changes. This was surprising in view of hemorrhagic and exudative lesions described by some authors.

IV. Direct intracardic injections of a strain of streptococcus isolated from the blood of a rabbit with sub acute bacterial endocarditis, were carried out in ten rabbits. Number of injections varied from three to nine.

Cause of death in all animals was a more or less gradual deposition of layers of clotted blood within the pericardial cavity distending it tremendously. Four rabbits developed a definite vegatative endocarditis. No glomerular lesions of any sort were encountered. In one of the rabbits that developed endocarditis a small infarct was found in one kidney.

V. Direct injection of a bacterial suspension (as in IV) with lycopoduim spores into the left renal artery was carried out successfully on twenty-six animals. They were allowed to live from 19-65 days when they were killed by a blow on the back of the neck, and necropsy was performed immediately.

The kidney in general showed rather uniform findings. Grossly there was a varying amount of pitting with wedge shaped cortical scars. Microscopic wedge shaped areas were found in the cortex with relatively wide bases, in which were seen tubular degeneration, atrophy and distortion, marked fibrosis between the tubules and around the glomeruli, often large masses of red cells near a vessel containing spores, and organized, canalized thrombus, and a varying number of spores in the arterioles,,vary rarely in the glomerulus. All of these changes could be attributed to the partial or complete obstruction

of arteries in the involved areas. In other words, there was a focal embolic process, the abstruction being due to the inert spores. The bacteria apparently played no important rale.

In this series the right kidney was left as the control. Fourteen of the twenty-six showed a varying amount of gross pitting. Three more showed microscopic scars and red cell infiltrations. This was described as a spontaneous nephritis, unless the findings could be attributed to the circulating bacteria originally injected into the opposite kidney. This did not seem plausible as two animals which died during operation showed these same findings in the right kidney as did one which received only spores. Whatever the cause of the pitting in the right kidney, the incidence was unusually high in this series.

VI. During the course of this experiment above, a simultaneous study was made of the histologic conditions of kidneys obtained from rabbits which happened to die in the laboratory. Some were unused, supposedly normal. Most of them had been injected with human serum, foreign protein, etc., in the course of work on precipitins. None had received bacteria of any sort. The kidney of twenty-four rabbits were

entirely normal, thirty-four showed a varying amount of focal cortical scarring and red cells infillration. In many of the thirty-four gross pitting was present. Thus 40% showed a spontaneous nephritis. Spontaneous nephritis is different from true form of chronic glomerular nephritis in that the latter ends in the so called granular or contracted kidney. In conclusion, Leiter (26) states. "Chronic glomerular nephritis has not yet been produced constantly or even frequently in an experimental animal. The rabbit is probably not a suitable animal for this purpose, because it does not react as does the human beings to the agents that can injure the glomeruli. My own attempts to produce a chronic lesion by means of bacteria along, bacteria with diphtheria toxin, bacteria with snake venom, or bacteria with spores, all calculated to damage the circulation within the glomeruli and introduce infection at the same time have been unsuccessful, although a large number of animals were used with each method of procedure. Whatever changes were observed in kidney could not be interpreted as those of glomerular nephritis, either acute or chronic."

STREPTOCOCCUS

From the forgoing discussion it is seen that, although the etiology of glomerular nephritis remains unknown, all studies indicate that a close relationship exists between certain infections and the onset of the disease. In a vast majority of instances acute nephritis follows infection of the upper respiratory thract and in cases where careful bacteriological and immunological observations have been made, it has become apparent that the hemolytic streptococcus, above all other organisms, is of prime improtance. In order that the etiology may be more accurately founded and the relative importance be attached to the various predisposing factors it is necessary that we have a clear understanding of the mechanism involved in the production of the disease. As a result numerous theories based on observation and experimental studies have been proposed.

Direct experimentation, so far, has not yielded conclusive corroborative results. Lesions in the glomeruli of animals sometimes described as glomerular nephritis have occassionally been observed following the introvenous injection of streptococci.

1917 Ophulus, 31 in his experiments with rabbits was unable to produce changes characteristic of glomerular

nephritis. He was unable to differentiate this type of change from the spontaneous type which he frequently observed in the control group.

In work described in the previous discussion Leiter has shown that experiments calculated to damage the circulation within the glomeruli and introduce infection at the same time have been unsuccessful, and the results could not be interpreted as those of glomerular nephritis.

The close association between nephritis and streptococcus was demonstrated by Le Count and Jackson. (25)

They were able todemonstrate fewer changes in the kidney of rabbitstreated with anti streptococcus serum or vaccine,than in those of the untreated animals. In their experiments 56% of the animals showed lymphocyte and plasma cell exudate. Assuming that some of these changes were of the spontaneous type, it is likely that the changes in a considerable number of the rabbits were due to the streptococcus.

Bell, Clawson and Hartzell, (37) some years later, again showed this definite realtion between the streptococcus and glomerular nephritis.

They experimented with rabbits and monkeys. Nonhemolytic strains of streptococcus were used. Twenty-five rabbits were given a large number of injections.

Renal lesions were frequently found, but alwasy of the spontaneous, or lymphocytic interstitial type.

Fourteen monkeys were given intravenous injections of this same streptococcus. Lesions were produced in the kidneys of five. Only one of these was glomerular nephritis. In the others there was no serious renal damage. No explanation of the varying effects of the organisms upon the kidney was offered. In an effort to explain the origin of nephritis Bell (7) offered these hypothese:

(1) Special etiological agent-perhaps a special strain of streptococcus

(2) Many kinds of streptococci may produce disease but only certain individuals are susceptible.

(3) There must be repeated injury to the glomerular endothelium. Indivudual ausceptibility or strain of infectious organisms are of little importance

Numerous experimenters have attempted to produce glomerular lesions by the intravenous injection of filtered products of the growth of streptococci.

Duvol and Hibbard (15) were among the first to experiment along this line.

Their experiments indicate that the active toxic principle of the streptococcus scarlatina is an endo toxin and not a secretory product of the living organism.

This was shown by the fact that after immunization of a rabbit, the intraperitoneal injection of a large amount of scarlatinal streptococcus will produce toxic symptoms and death in from 2 to 24 hours; whereas the pritoneal injection of a similar quantity into the rabbit which has not been immunized has no appreciable effect. It was thought the endo toxin was liberated by the special bacteriolysin present in the immunized animal. They procured this endo toxic, or bacteriolysate, as they called it, from the peritoneal cavity of an immune rabbit which had been given a large dose of streptococcus culture. In from 1 to 2 hours followingintraperitioneal injection the animal was sacraficed and culture material from the cavity collocted.

By subcutaneous, introvenous, and intraperitoneal injections of this lysate into rabbirs they were able to produce nephritis--the lesions of which were analogous in kind and variety to those of acute scarlatinal nephritis in man, including the epithelial crescent formation, hyaline thrombi of he glomerular capularies, hemmorrhage into the capsular space and necrosis of the tufts. The intravenous method of injection seemed to be the most effective inthe production of the acu te glomerular nephritis. These experiments would then seem

to constitue evidence of the possible specific relationship of the streptococcus in scarletena, to the frequently associated glomerular nephritis; however, this is not proof that the hemolytic streptococcus is the only cause of the disease.

Gray,[20] by a series of animal experiments has evidence much in favor of the bacteria toxic origin of the glomerular nephritis. Inthis type of nephritis, the bacterial factor is provided by the lysis of organisms trapped in the glomeruli with consequent release of endo toxin. On the basis of modern renal function the toxins being colloids are not filtered through the healthy glomerular tuft and so are concentrated in the glomeruli by withdrawl of fluid in the filtrate; hence the nephritis is initially glomerular.

Longcope[30] 1929 showed that all the strains of the streptococcus used in his experiments produced so called toxic filtrates often of considerable potency and it seems possible that such toxins liberated by growth of streptococcus and eliminated through kidney might cause glomerular nephritis in patients rendered highly susceptible in some way to these toxins.

In more recent experiments Longcope[30] 1929 and his workers prepared a bouillion filtrate of hemolytic streptococcus and tested the skin reactions of persons

apparently normal, of those suffering from acute tonsillitis and of those suffering from acute and sub-acute glomerular nephritis, they found some increase of skin reactions, over normal, in acute tonsillitis, but that it was definitely exaggerated in nephritis. Whereas a normal individual may react to 1 to 100 dilution, many of nephritic patients react s trongly to 1 to 2000. From this it would seem that these pronounced reactions indicate that these patients have acquired, or posses a high degree of allergy toward some substance of H. strep. or in the products of their growth.

In view of the frequency with which glomerular nephritis occurs with endocarditis, and because they questioned the embolic nature of glomerular nephirtis, Rich and his workers sought to show that the high incidence of glomerular nephritis in endocarditis might be referrable to the action of toxinsproduced by themicroorganism in question, rather than emboli. Using a sterile bacterial free filtrate from a patient suffering from endocarditis and showing signs of renal damage, he was able to produce, in 21% of the rabbits, (79 used in experiment) glomerular damage which he interpreted as being comparable to acute glomerular nephritis; although others have commented upon the frequency of spontaneous nephritis, he states they have never encountered a case, and their

control series (90 rabbits) were free from it. Whether or not they were dealing with a true toxin could not be stated; however, they were certain that the renal damage had nothing to do with allergy.

There is no evidence to show that diffuse glomerular nephritis is caused either by the lodgment of streptococci in the glomerular capillaries, or by the direct action of acteria in the kidney. Careful and repeated cultures from large amounts of urine in studies of many patients have yielded negative results. Cultures from the blood stream at the onset of the disease and during its course have given negative results, and streptococci have not been found in sections of the kidney.

It hasbeen the rather popular conception that toxins elaborated by streptococci at the site of the infection and excreted through the kidney may be directly responsible for the kidney lesions. Evidence points against this concept of immediate damage to the kidney by the bacterial products, because of the fact that acute glomerular nephirits follows, rather than accompanies the acute infection. Peters (**) supports this view with the statement that nephritis manifests itself in the 2nd, 3rd or 4th week after the onset of scarlatina; at this time toxic manifestations have

ceases and there is presumable an excess of anti toxin in the blood. He also states that persons immune to the disease may never the less become infected with scarlatina streptococcus and develop a typical nephritis.

Lyttle (33) observed the sediment count on a carefully controlled group of patients with scarlet fever. In none ofthese cases did nephritis develop. Five patients received from 2-1200 units of anti toxin before the 5th day of the disease. Serum reactions were noted on the 6th, 7th, 8th and 9th day following the injections. These patients did not show, at a later date, dediment counts different from those presented by patientswho received no serum. During the period from 8-45 days after onset, all cases showed in varying degrees an increase in the excretion of protein, casts and cells. These were all qualatative changes which take place in nephritis and which occurred at the time past scarlatinal nephritis is most likely to develop. In view of this it appeared likely that the same mechanism is at work in both conditions. From these observations he sugges ed that the majority of individuals who contract scarlet fever make a satisfactory immunological adjustment in the post febrile period. Hence kidney damage is slight and shown only

by careful examination of the urine. In other words the nephritis is aborted. Individuals unable to make this adjustment develop true post scarlatinal nephritis.

Though it is difficult to measure with accuracy the time interval between the onset of tonsillitis, sinusitis etc, and the onset of nephritis, it rarely happens that the two conditionsappear simultaneously, for the first symptoms and signs of acute nephritis are usually observed during convalescence or at least several days after the onset of the acute infection. It wasthis time relationship which led Von Pirquet (46) to draw an analogy between the specific complications of scarlet fever, such as acute nephritis, and the occurrence of serum disease following one to two weeks after the theraputic administration of horse serum. Von Pirquet (46) states that Schick (1903),by an exact observation of very many cases of scarlet fever noted the following:

(1) That nephritis is only one of the typical sequela--equivalent and often very closely combined are; lymphadenitic affections of the regional glands, characteristic, rises of scarlet fever.

These were interpreted as probably being local repitition of the primary process. It was

It was suggested that the disappearance of the rash, and are able to produce a new infection or toxic action during the period of predis position, which is to be explained as a hypersensibility of the organism.

As mentioned previously, Loncope (36) later supported this conclusion.

Friedmam and Deicher (35) in 1928 found the serum of scarlet fever patients; with nephritis; contained in the third week week of scarlet fever an extra ordinarily large amount of anti bodies, whereas the serum of scarlet fever convalescents with out nephritis contained in the 3rd week an extremely small amount. They did not find that anti bodies appeared more abundantly in the serum of scarlet fever patients with septic complications than in serums of patients with uncomplicated scarlet fever. They believe then h the premature anti formation to be the cause of nephritis. They suggest the following hypothesis:

By the action of anti bodies on the streptococcus endotoxins are set free, and these are the cause of nephritis. Anti endotoxins are also produced which are able to neutralize the action of the endotoxin. As a usual thing, the antitoxins are produced at the same time as, or earlier than, the anti bacterial anti bodies.

In a certain number of patients the anti bodies appear very early and the formation of anti toxins does not keep pace with them. These are the patients who develop nephritis.

In 1931 Baehr (3) proposed that the products of cell destruction caused by damage to renal parenchyma during scarlet fever might act anti genically during convalescence and give rise to nephritis, no matter how prolonged unless the streptococcus are killed off and pa ient recovers from the infection. These findings were based on careful observation of Streptococcus Hemolyticus bacteremia. In those cases in which the organisms were repeatedly found in the blood no cases of glomerular nephritis were reported. In those patients who apparently recovered from the infection, glomerular nephritis was responsible for urenic death in 33.3% of the cases; another 1/3 died in in sub-acute or chronic stages of glomerular nephritis

Kellett (24) in experimenting with blood compliment estimations found that in three cases of glomerular nephritis the blood compliment was much lower than normal but gradually returned with recovery. No such drop was seenin chronic nephirits. In way of an explanation he suggested that seversed anaphylaxis might be the underlying mechanism of glomerular nephritis--

reversed anaphylaxis Kellett (24) defined as shock dependant on a reaction between circulatory anti bodies and antigen fixed to the cell.

Upon this hypothesis ofreversed anaphylaxis Kellett (24) suggested that acute glomerular nephritis may be a condition, essentically generalized, resulting from a reaction between anti bodies elaborated by the body and toxins elaborated by the orginanisms that plaved a part in the original infection; the toxins having been fixed in some way to the tissue cells and more particularly those of the kidney inwwhich they would be concentrated and through which hey are known to be excreted. The kidneys may therefore be expected to suffer the greatest damage, and glomerular nephritis will arise in patients in whom anti bodies, prematurely formed can be demonstrated.

In 1908 Pearce (37) noted that the serum of animal suffering from an experimental chromate nephritis has the power to produce lesions of the kidney when injected into a normal animal. Dogs were used, and eight cases of nephritis were produced by this method.

Smadel (43) states that Linderman was the first to use anti kidney serum experimentally.

Quote from Cecil (12): "In 1928 Masugi demonstrated that an anti kidney serum, produced by the injection of

rat kidney emulsion into rabbits, when injected into rats gives rise to acute or chronic nephritis--" These results have been confirmed and greatly extended by Smodel and Farr (43).

The preparation of their anti sera was a rather complicated procedure. Inorder to avoid reactions from serum, red blood cells, etc. the organs were thoroughly profused with normal saline and all blood was washed from the organ.

The anti kidney serum was prepared in the rabbit by immunization with a saline suspension of this perfused rat kidney.

There experiments were as follows:

Group I Eight rats received a total of 3 cc/100 gms. body weight of anti kidney serum in divided doses, over several weeks.

Two rabbits received .45 cc/100 gms. body weight. They received two injections on consecutive days.

Group II Two rats were given .65 cc/100 gms. body weight--four divided doses at four day intervals.

Group III Two rats were untreated.

Two rats were given the serum of a rabbit in with rat serum.

Two rats received anti kidney serum completely absorbed by rat kidney or liver. All of the rats which received anti kidney serum, except the last two in group III, bowed elinically severe albuminuira, cylindersia, anasarca but not hematuria.

Rapidly fatal nephritis results by injecting relatively large amounts of kidney serum at frequent in ervals. The smaller dose injected the milder becomes the nephritis.

The majority of rats which survived the initial stage of this experimental glomerular nephritis continued to show marked albuminuria with casts until they died or were sacaraficed months later. The terminal picture wasmuch like that of the terminal stage of glomerular nephritis--retention of urea, plasma protein deficiet, anemia, and hypertension.

They were able to verify these results in more recent experiments. Although they discovered no new lesion but did differentiate the early histiological effects of the nephrotoxin from those of the non organ specific tissue anti bodies.

They were unable whether the endothelial proliferat on was attributable to the nephrotoxic or anaphylactoid effect.

Swift and Smadel (45) have shown that a saline extract of perfused rat kidney administered intravenously to rats immediately before injecting an anti rat kidney serum by the same route , prevents renal damage--a preliminary injection of physological salt solution or of an extract of perfused rat liver has no preventative effect.

This seems to show rather definietly that the nephrotoxic effect induced by anti rat kidney serum is dependant on a relatively organ specific anti body nephrotoxin.

SUMMARY

In conclusion, then, one may summarize the information, concerning the etiology of glomerular nephritis, presented in this discussion as follows: the true glomerular nephritis follows acute infections, proven to be due in such a large proportion of instances to haemolytic streptococci, that at present it seems justifiable to consider, at least one variety of acute glomerular nephritis, as a manifestation of streptococci infection. Experimental results as well as accurate observations, with ehemicals and poison fail to show that they will result in a true inflamatory process in the glomeruli. Predis posing factors, especially exposure to cold, may have a definite etiologic role. It can not be proven that the acute glomerular nephritis depends upon infection by a particular form of streptococcus, or upon the invasion of the blood or the involvement of the kidney by streptococci.

There is some evidence-however- which indicate that patients suffering from acute nephritis are abnormally susceptible to the products of the growth of hemolytic streptococci; and it seems possible that some altered reaction of the tissue such as occurs in allergy, or some unusually antibody response to the infection is the dermining factor in the development of acute glomerular nephritis in individual cases.

From the experiments with Anti kidney serum, it appears

that the ~~haemolytic~~ streptococcus produces with in suscenptible individuals nephrotoxic immune bodies. There then may give rise to actue or ehronic nephritis -- It is in relation to the latter form that it is a possible explanation for the cases of ehronic progressive glomerular nephritis in which most rigid elimcal, bacteriological and immunological studies fail to produce e vidence for the persistence or recurrence of streptococcal infection to account for the relentless progression of desease; however this is of little value in those ehronic eases which begin insidiously and with out apparent relation to a recognized preceding infections process.

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