RELATIONSHIP OF ACUTE INFECTIONS TO GLOMERULAR NEPHRITIS[1]

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The etiological relationship of infections to the diffuse form of acute and subacute nephritis is a problem which for many years has commanded attention, but has rarely received more than casuistic study. Löhlein (a) in 1907 described in detail the early lesions of the glomeruli in acute glomerular nephritis, as well as the subsequent changes that took place in the kidney during the subacute and chronic stages of the disease. Since a large proportion of his cases of acute and subacute nephritis occurred in patients suffering from various forms of infection, usually due to streptococci, he concluded that in the vast majority of cases acute glomerular nephritis was the direct result of streptococcus infection. Fahr (1912), somewhat later, pointed out the frequency with which acute glomerular nephritis was preceded or accompanied by infections particularly those due to streptococci, while Volhard and Fahr (1914) state that in their collected cases one quarter of all those nephritides associated with infections followed tonsillitis, and almost three quarters, 125 of 179, were connected with infections of the upper respiratory tract. Of a total of 67 cases of acute diffuse glomerular nephritis, 44 suffered from angina, scarlatina, wound infections or erysipelas. In general most of the statistical evidence that can be obtained (Hill (1919); Bell and Hartzell (1922); Kuczynski (1919a); Stolz (1925); Blackfan (1926)) tends to confirm the fact that streptococcus infections and especially tonsillitis precede directly or accompany the onset of a considerable number of cases of acute diffuse glomerular nephritis. Infections due to other or-

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ganisms, such as the pneumococcus, are also recorded in this relationship, but as compared to scarlatina and other streptococcus infections they are comparatively infrequent.

A number of observers, however, including Munk (1916a and b) have not been inclined to accord much importance to the streptococcus, or other known bacteria, in the etiology of acute nephritis. Though recognizing the close relationship that is often found to exist between glomerular nephritis and many forms of streptococcus infection they consider the actual cause of this form of nephritis unknown.

Attempts to produce glomerular nephritis in animals by the injection of streptococci have been only partially successful. Ophüls (1917), who upholds the infectious origin of glomerular nephritis, reports the production of glomerular lesions in 14 of 48 rabbits injected intravenously with cultures of streptococci. Kuczynski (a) made repeated injections of streptococci into mice and believed that by this method he could produce glomerular lesions similar to those observed in man. Bell, Clawson and Hartzell (1925) report the results of repeated injections of hemolytic and non-hemolytic streptococci in 14 monkeys. In two animals there developed a severe nephrosis; in one an interstitial nephritis, while in one monkey injected repeatedly with cultures of *Streptococcus viridans*, there occurred an acute glomerular nephritis. Duval and Hibbard (1926) state that they can produce injury to glomeruli in rabbits by the injection of certain lytic products of *Streptococcus scarlatinae.*

In evaluating the importance of these experiments it is necessary to bear in mind the essential difference, so clearly recognized by Löhlein (1910b) and Volhard and Fahr and now so generally accepted, between the diffuse and the focal form of glomerular nephritis. The latter occurs with great frequency in subacute bacterial endocarditis, is undoubtedly due to the deposition of *Streptococcus viridans* in the glomeruli, and has been quite accurately reproduced experimentally by Kinsella and Sherburn (1922) and by Clawson (1926) in dogs whose heart valves have been infected with *Streptococcus viridans.* Though Kuczynski (1919a) has suggested that the diffuse form of glomerular nephritis may in some instances be caused by the transportation of the bodies of streptococci to the kidney where they are engulfed by the cells lining the glomeruli and there set up a diffuse progressive

inflammation, it has been the idea of other observers (Schridde (1913)) that the diffuse lesions in the glomeruli are caused by the elimination of a toxin, produced by streptococci or by other bacteria in a focus of infection distant from the kidney.

The demonstration by Dochez (1924) and by Dick and Dick (1921a) that a type of hemolytic streptococcus is the cause of scarlet fever adds fresh incentive to investigations on this problem, for the post scaratinal nephritis has always been considered as the prototype of the diffuse glomerular variety. The experiments, moreover, of Dick and Dick (1924b) on the elaboration of a filterable "toxin" by *Streptococcus scarlatinae* indicate still further methods which might be applicable to studies upon nephritis.

It has seemed to us important to investigate two phases of the problem, first the relationship of acute infections to the onset of glomerular nephritis, and secondly the relation of infections to the progress of nephritis. If streptococcus infections of the upper respiratory tract, such as tonsillitis, sinusitis, etc., are directly responsible for the onset of glomerular nephritis, the progress of the disease might bear some relationship to the course of the infection. With the subsidence of the infection and disappearance of the infecting organism one might expect recovery from the nephritis, provided the kidney itself is not the seat of active bacterial growth; while progression of the nephritis to a subacute or chronic stage might be accompanied by persistence or exacerbations of the infection such as those of the upper respiratory tract, or at least by the continued presence of the infecting organism in these situations.

With this idea in mind it has been possible to study forty cases of acute or subacute glomerular nephritis in young adults, and in twenty-seven of these to follow the course of the disease with some care over a period varying from a few months to four years. Cases of focal nephritis occurring in bacterial endocarditis were excluded.

The ages of the patients were as shown on page 4.

Most patients were seen within a few days to a few weeks of the apparent onset of their disease, while a few developed the disease under observation. Daily variations in the clinical course of the disease were recorded with daily observations of the urine and blood pressure, frequent examination of the fundus oculi, and repeated determinations

of renal function. Cultures were made from any obvious infection. The accessory nasal sinuses were always examined, and we are greatly indebted to Dr. Crowe and his staff for their assistance in this connection, and for the operative procedures which they have performed on these patients. When it was not possible to detect an obvious acute infection after a careful search, cultures were made by the swab method from the tonsils, pharynx and naso-pharynx, and from the tonsils by the pipette method used by Bloomfield and Felty (1923). Cultures were repeated during the course of the disease, during convalescence and after recovery. The swab method was employed to obtain cultures from the pharynx and fauces of the patients who were tonsillectomized. The urine from patients during the acute and subacute stages of the disease was cultured in amounts of 1 cc.

Age of patients

Age	Number
1–10	1
10–20	14
20–30	14
30–35	5
35–	6
	40

to 5 cc. Blood cultures were made from those patients who had fever. Blood agar was employed routinely as a medium.

Table 1 shows the incidence of definite acute infections occurring at the onset of nephritis in the entire group of 40 patients, and table 2 records the variety of infection with the results of the bacteriological examination of these infections.

Though the actual incidence of infection is very high there still remains 15 per cent in whom no definite infection could be found. In some of these an insignificant focus might have escaped detection, but in at least two cases of subacute glomerular nephritis that died and came to autopsy, it was impossible either during life or after death to demonstrate an associated infection. The figures in table 2 confirm the observations of others as to the frequency of tonsillitis and infections of the upper respiratory tract in connection with the

onset of acute nephritis. Tonsillitis occurred in almost 53 per cent of the cases, while infections of the accessory nasal sinuses, throat and respiratory tract taken together were found in 85 per cent. It is also obvious that hemolytic streptococci prevail as a cause of these infections, since they occurred in 81.2 per cent of the infections studied bacteriologically.

The time interval between theo nset of the acute infection and the onset of the nephritis varied considerably in the different cases and could not always be definitely determined. In one case (IV) recurring infections probably due to hemolytic streptococci of β type had preceded the apparent onset of nephritis for three months. In another case infection of the tonsils and antra due to hemolytic streptococci had been almost continuous for three months when the patient developed acute nephritis while under observation. In other cases

TABLE 1

Incidence of acute infections at onset of 40 cases of acute and subacute nephritis

Number of cases	Infections present		Infections absent	
	Number	Per cent	Number	Per cent
40	34	85	6	15

the apparent interval was not more than ten days and in some cases the infection was unrecognized by the patient and was first discovered at the physical examination.

In order to investigate the second phase of this problem an attempt was made to study these patients more or less continuously over long periods of time. This has been accomplished with considerable success in 27 of the 34 patients in whom the onset of acute nephritis was directly preceded or accompanied by an acute infection.

These 27 cases have been divided into two groups, first those who, as far as can be determined, have recovered from the attack of acute nephritis, and secondly, those who still show evidence of nephritis, or in whom the disease has definitely progressed or has terminated fatally.

In the first group there were 14 patients, 9 of whom had an acute tonsillitis due in 5 instances to hemolytic streptococci of β type, and in one to streptococci of α type. In two instances cultures were not

made during the acute attack. One patient had acute tonsillitis associated with broncho-pneumonia due to hemolytic streptococci of β type, two patients had broncho-pneumonia due to hemolytic streptococci, and two patient sinusitis, one due to hemolytic streptococci

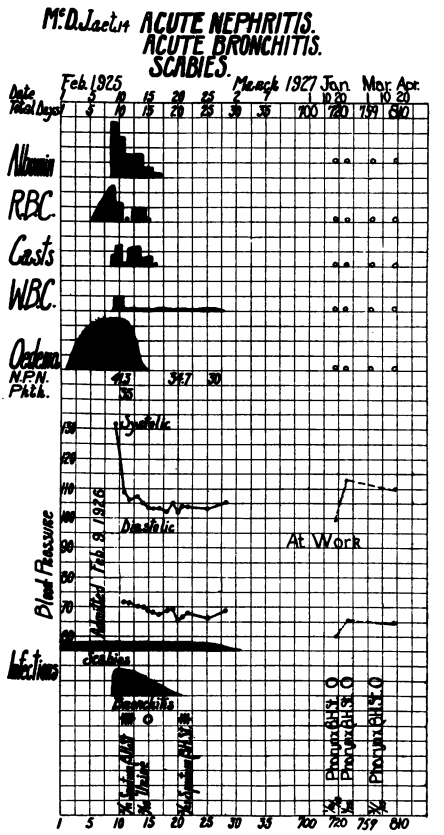

CHART I. Case I, showing the results of urinary examinations, the degree of edema, the non-protein nitrogen of blood, and phthalein excretion, the changes in systolic and diastolic blood pressure, the duration of infections and the results of bacteriological examinations charted chronologically.

of β type and one to Pneumococcus type IV. In seven of the cases of tonsillitis, tonsillectomy was performed. In two of these the excised tonsils were obtained for culture and showed a pure growth of hemolytic streptococci. In the two cases of sinusitis, cultures were

obtained from the antra and the ethmoidal sinuses at operation. The following abstracts and charts indicate the course of the disease and the results of repeated cultures in four cases of this group.

Case I. McD. J., male, white, aet. 14. Admitted to the Johns Hopkins Hospital February 9, 1925, complaining of bad cold and kidney "trouble." He had had measles, mumps and nasal operation at 4. Three attacks of tonsillitis in 2 years. Two weeks before admission developed scabies; one week before admission swelling of face, anorexia, vertigo and vomiting. A few days before admission voided bloody urine. Examination showed slight pallor, moderate edema about the eyes and face and over shins, scabies, numerous râles throughout both lungs. Heart and abdomen normal. Blood pressure 132/95. Temperature 99.5° Pulse 90. Albuminuria, hematuria, and cylindruria. Hemoglobin 62 per cent. Red blood cells 3,280,000, white blood cells 6,800. Wassermann reaction negative. X-ray of chest showed "extensive shadows through both lungs." February 11, culture of sputum showed great numbers of hemolytic streptococci of β type. By February 12 the edema had disappeared; râles still persisted in the chest; cultures of the urine showed no growth. On February 21 cultures of sputum showed hemolytic streptococci still predominating. Discharged March 4. Has remained well for 2 years. During January, February and April 1927, physical examination showed nothing abnormal; the urine has been normal; the blood pressure 110/70 and cultures from the pharynx have not shown hemolytic streptococci of β type. Chart I.

Summary: A mild case of acute nephritis in a boy of 14 suffering from broncho-pneumonia due to hemolytic streptococci of β type. There was edema of the face, transient slight hypertension, albuminuria, hematuria, cylindruria, with some increase in blood non-protein nitrogen and decrease in phthalein excretion. Rapid recovery. In good health for 2 years and 3 months after attack, with normal urine, normal blood pressure, and pharynx and tonsils free from hemolytic streptococci of β type.

Case II. L. S., male, white, single, aet. 21, printer. Admitted to the Johns Hopkins Hospital February 26, 1926 complaining of bloody urine. Measles, mumps and pertussis, broncho-pneumonia at 12, tonsillitis at 17. Urethral discharge for 2 months. No scarlet fever or diphtheria. Severe sore throat from December 26, 1925 to January 3, 1926; hematuria with nausea and vomiting during first week in January; for three weeks before admission swelling of face and feet. Examination showed edema of face, swollen red tonsils, enlargement of submaxillary lymph nodes; normal fundi, moderate hypertension (140/90, albuminuria, hematuria, cylindruria. Hemoglobin 85 per cent; red blood cells

5,440,000; white blood cells 10,040; Wassermann reaction negative; Temperature 98.6°. Culture from tonsils shows hemolytic streptococci of β type. By February 10 general improvement, less edema, right fundus shows two small patches of exudate. During following week rapid improvement. February 17 tonsillectomy; cultures from excised tonsils give pure growth of hemolytic streptococci of β type. February 2, temperature 102.6°; throat very sore. February 22, white blood cells 17,520; February 24 return of edema, increase in red blood cells in urine; infection of right nostril and purulent discharge; culture from nasal discharge gives hemolytic streptococci of β type; February 28 improved; edema

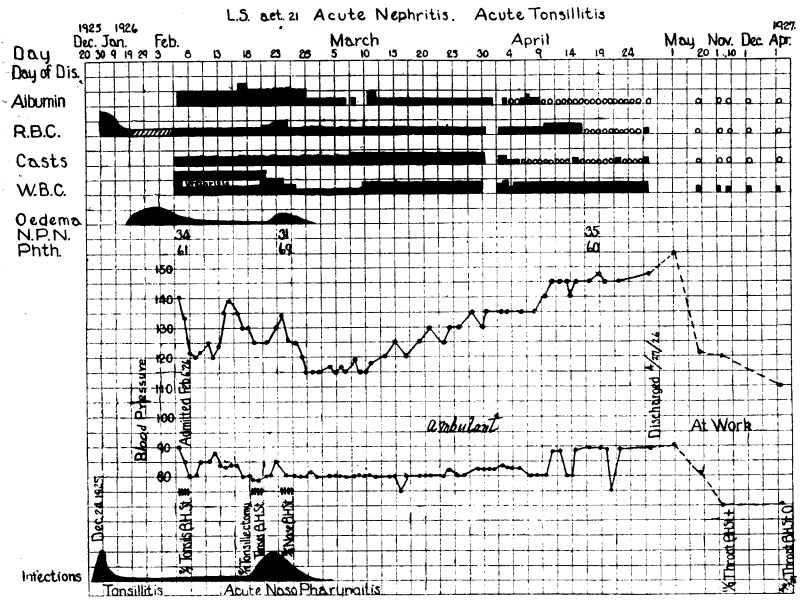

CHART II. Case II, showing the results of urine examinations, the non-protein nitrogen of blood and phthalein excretion, the changes in systolic and diastolic blood pressure, the bacteriological examinations and course of the infection charted chronologically.

disappeared; discharge from nostril diminished; temperature has gradually fallen to 100°; white blood cells 11,120. Continuous improvement until discharge April 27 with no edema, blood pressure 128/80 and no albumin, red blood cells or casts in urine. After discharge the blood pressure rose temporarily though patient felt well, and urine was normal. Examinations made in November and December 1926 and in April 1927 have shown the patient to be normal. The blood pressure has been 120/70; the urine has not shown albumin, red blood cells or casts. Cultures from the throat have not shown hemolytic streptococci, since November 9, 1926. Chart II.

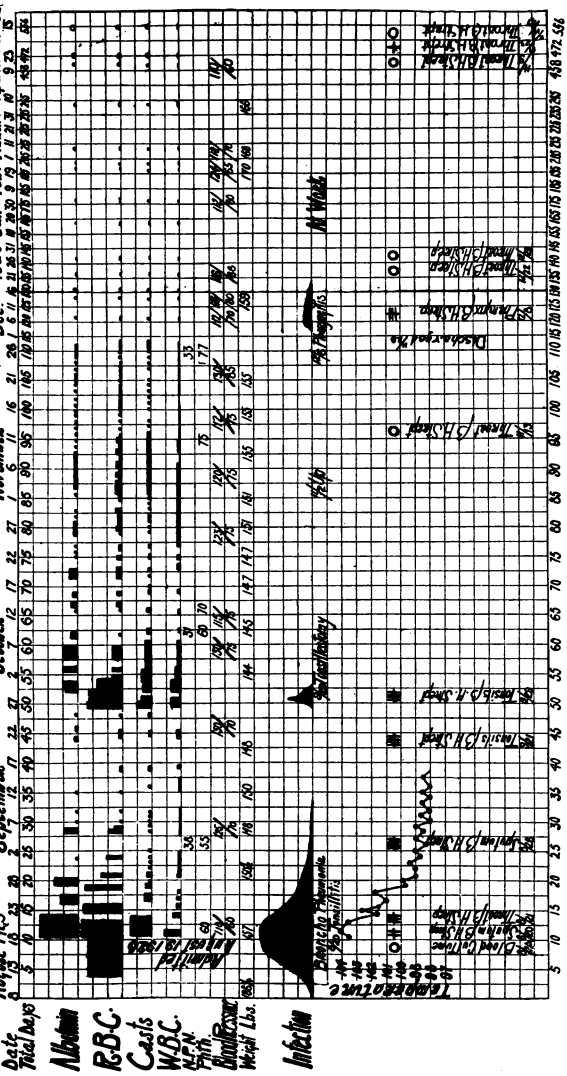

CHART III. Case III, showing the results of urine examinations, the non-protein nitrogen of blood and phthalein excretion, the blood pressure, weight, the course of infections, the temperature and results of bacteriological examinations charted chronologically.

Summary: A case of acute nephritis in a young white man with acute tonsillitis due to hemolytic streptococci of β type; moderate edema, hypertension, albuminuria, hematuria and cylindruria, transient changes in fundi. Normal blood non-protein nitrogen and phthalein excretion; rapid improvement. Tonsillectomy followed by infection of naso-pharynx and nares by hemolytic streptococci of β type with exacerbation of nephritis. Transient elevation of blood pressure after discharge with eventual recovery. In good health one year after attack with normal urine and blood pressure and no growth of hemolytic streptococci of β type in pharyngeal cultures.

Case III. A. McC., male, white, married, aet. 23, painter. Admitted to Johns Hopkins Hospital August 19, 1925 complaining of pain in chest. He had pneumonia at 2, measles, mumps and pertussis as a child, and frequent colds. Ten days before admission epigastric pain, frequent cough, with dark urine for 6 days. Examination showed temperature 102°; pulse 96; aspirations 32. Acutely ill; enlargement of tonsils; no facial or subcutaneous edema; signs of partial solidification of right upper lobe. Blood pressure 110/60; albuminuria, hematuria, cylindruria; white blood cells 17,000. August 2, cultures from sputum show hemolytic streptococci of β type; no pneumococci; blood cultures negative. August 21, continuous fever from 101.8° to 103.6°; tonsils acutely swollen; cultures give hemolytic streptococci of β type. August 25 patient much improved. Temperature 99° to 101°. Urine culture shows no growth. September 28 throat and tonsils swollen; pain in back; gross hematuria. September 29 tonsillectomy; cultures from tonsils give profuse growth of hemolytic streptococci of β type. October 7, fundi normal; slow convalescence. October 14, urine culture gave no growth. November 28 discharged much improved. December 8, mild pharyngitis, otherwise well; cultures from pharynx show hemolytic streptococci of β type. Has remained well for 18 months. The blood pressure has been normal, the urine free from albumin, casts and red blood cells; cultures from the pharynx have not shown hemolytic streptococci since December 1925, except on one occasion when they were present in small numbers. Chart III.

Summary: A case of acute nephritis in a young white man suffering from acute broncho-pneumonia and chronic tonsillitis due to hemolytic streptococci. No edema or hypertension, blood non-protein nitrogen and phthalein excretion normal; albuminuria, hematuria and cylindruria. Acute tonsillitis due to hemolytic streptococci of β type during convalescence with exacerbation of nephritis. Tonsillectomy. Gradual disappearance of blood and albumin from urine. Recovered and in excellent health 1½ years after attack with normal

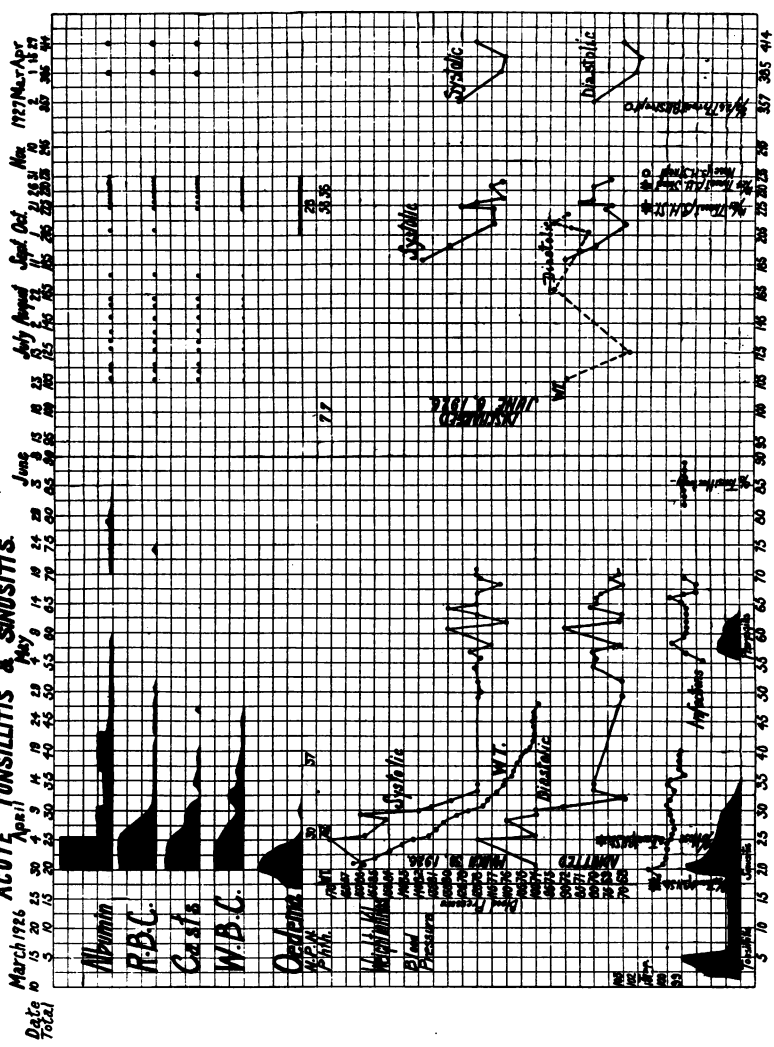

CHART IV. Case IV C. T., showing the results of urine examinations, the degree of edema, the non-protein nitrogen of blood and phthalein excretion, the changes in systolic and diastolic blood pressure, the changes in weight and temperature, the results of bacteriological examinations and the course of infections charted chronologically.

urine and blood pressure. Repeated cultures from pharynx show no hemolytic streptococci of β type.

Case IV. C. T., female, white, single, aet. 28. Admitted to the Johns Hopkins Hospital March 3, 1926 complaining of swelling about eyes. Measles during childhood; diphtheria in 1916; tonsillitis in 1917, 1920, 1921 and 1922. No scarlatina; numerous attacks of coryza. In January 1926 severe cold for 3 weeks. March 11, sore throat with chill, headache, nausea and vomiting; recovery in 6 days. March 26, swelling of eyes with morning nausea, continuing to admission. Examination showed anasarca, scarred tonsils, tender submaxillary nodes, purulent infection of right antrum, lungs normal, cardiac impulse forceful, reduplication of first sound at apex. Blood pressure 160/100. Fundi normal. Albuminuria, cylindruria and hematuria. Temperature 100°; Pulse 100; Hemoglobin 74 per cent; red blood cells 3,872,000; white blood cells 8,400; cultures from tonsils show hemolytic streptococci of β type; cultures from urine no growth. April 1, right antrum irrigated; anasarca decreased. Temperature 99.4° to 100°. April 5 culture from nostrils give hemolytic streptococci of β type. April 13 infection healed; temperature normal; no edema; urine contains traces of albumin, occasional hyaline cast and white blood cells. June 3, tonsillectomy followed by uneventful recovery. Patient has remained well with normal urine and blood pressure (110/64–126/80) to May 1927. Cultures from pharynx on October 21, 1926 and October 28, 1926 still showed moderate numbers of hemolytic streptococci of β type. Cultures from the pharynx on March 2, 1927 showed no hemolytic streptococci. Chart IV.

Summary: A case of acute nephritis in a young white woman, preceded by acute tonsillitis and accompanied by sinusitis due to hemolytic streptococci of β type, anasarca, hypertension, albuminuria, hematuria and cylindruria; normal non-protein nitrogen and phthalein excretion. Drainage of sinuses. Recovery from the infection and rapid convalescence from nephritis. Tonsillectomy. In excellent health one year later. Urine and blood pressure normal. Cultures from pharynx 4 months after attack still showed hemolytic streptococci of β type. Cultures from pharynx after one year showed no hemolytic streptococci.

The preceding protocols and charts illustrate the course of the disease as it occurred in 10 of the 14 cases that have apparently recovered from the attack of acute nephritis. Four of the 14 cases report themselves as being well, but have not been properly studied since recovery. Of the ten cases that have been carefully studied, nine or 90 per cent are free from infections of the upper respiratory

tract one to four years after the attacks of nephritis, and cultures have shown that the fauces and nasopharynx are free of the organisms originally producing the infection. One of the ten patients has remained a carrier of hemolytic streptococci of β type.

During the convalescence from the disease in this group of patients, the mild exacerbations of nephritis, so frequently described, were observed in several. These are illustrated in the charts of cases II and III. They were observed to accompany a recrudescence or an extension of the infection. One patient suffered four such exacerbations of nephritis during a period of six months. Each exacerbation was related directly to the recurrence of a mild attack of tonsillitis due to hemolytic streptococci of β type. Removal of the tonsils has been followed by apparent recovery.

There is an obvious criticism of the results recorded in this group of patients. It may be argued, as Addis has done, that in spite of the excellent health of these individuals the nephritis remains latent, unrecognizable by ordinary methods, but slowly progressive. In order to detect abnormal elements in the urinary sediment in such patients Addis has devised a concentration test and believes by this means that it is possible to recognize a latent stage of the disease which may be present for years. We have not had an opportunity to employ this test except in one or two instances, but on these occasions the urinary sediment could not be differentiated from that of normal persons. In other respects, however, it has been possible to confirm in detail the changes that Addis has described as taking place in the character and numbers of the cells and casts of the urinary sediment during the subsidence of the acute stage of the disease, or during the progression of the acute to the chronic or terminal stage. It may be said, however, that by the usual methods of examination it has not been possible to detect evidence of disease in these patients who have apparently recovered. Moreover the contrast between this group and the following is so great that there seems justification in making a sharp distinction between them.

The second group consists of 13 patients whose disease progressed to a chronic stage or to a fatal termination. The same means were employed when possible to eradicate the infection in these patients as in the first group. One case of post scarlatinal nephritis with all

the evidences of chronic nephritis could not be followed carefully but is still living one year after the attack of scarlet fever. Of the remaining 12 cases, 4 had tonsillitis due to hemolytic streptococci of β type; 3 had tonsillitis and sinusitis in one case due to hemolytic streptococci of β type and in 2 cases due to streptococci of α type, 2 had

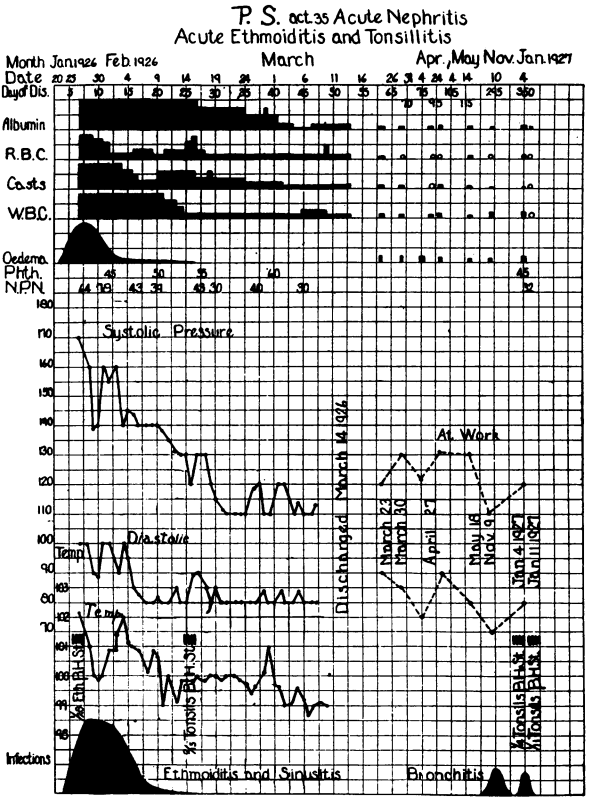

CHART V. Case V, showing the results of urine examinations, the course of edema, the phthalein excretion and non-protein nitrogen of the blood, the changes in systolic and diastolic blood pressure, the temperature curve, the results of bacteriological examinations and the course of infections charted chronologically.

sinusitis due to hemolytic streptococci of β type, one had tonsillitis due to hemolytic streptococci of β type combined with cystitis due to gonococci, and one had broncho-pneumonia the cause of which was not clear. Death occurred in this last patient, as well as in the patient suffering from gonococcal cystitis and in one case of sphenoiditis due

to hemolytic streptococci. Autopsy obtained in the first two cases showed acute and subacute diffuse glomerular nephritis.

Tonsillectomy and adenoidectomy was performed in six cases. In two of these, operations upon infected sinuses were also performed. In three cases the accessory nasal sinuses were punctured and drained. One patient refused tonsillectomy.

The following protocols and charts are examples of the changes observed during the course of the disease, and give the results of bacteriological examinations in this second group of 13 patients.

Case V. P. S., male, white, aet. 35, mill worker. Admitted to the Johns Hopkins Hospital January 27, 1926 complaining of swelling of body. Pneumonia three times before age of 7, double otitis media in childhood; no scarlatina or diphtheria. On January 23rd, sudden swelling of eyes, face and feet; temperature of 102.5°, cough, epistaxis, discharge from nose, dyspnea, weakness and suppression of urine. Examination showed anasarca, subconjunctival hemorrhage on right, reddened pharynx, purulent discharge from ethmoidal regions, numerous râles throughtout lungs; heart normal, blood pressure 180/100; acute urethritis; small quantities of dark urine with albuminuria, hematuria and cylindruria. Hemoglobin 85 per cent; red blood cells 5,510,000; white blood cells 11,800; increase in blood non-protein nitrogen to 78 mgm. per 100 cc. Cultures from ethmoidal region show hemolytic streptococci of β type. January 28 blood culture no growth; temperature 102.6°; pulse 110. Antra irrigated, sinuses drained. Fundi show edema of retina, blurring of disc margins and enlargement of veins. Rapid improvement after February 4 with diuresis and disappearance of edema; fall in blood pressure, subsidence of sinus infection, fall in temperature to normal by February 10, reduction in blood non-protein nitrogen to normal. Discharged March 14 in excellent condition, without edema, blood pressure 120/80, and without physical abnormalities except for slight albuminura and the occasional presence of red blood cells, casts and many white blood cells in the urine. In November 1926 and January 1927, one year after the attack, occasional edema of the feet, slight albuminuria and cylindruria persist. Cultures from tonsils show many hemolytic streptococci of β type. Chart V.

Summary: A case of acute nephritis in a white man associated with acute tonsillitis and sinusitis due to hemolytic streptococci of β type. Fever, anasarca, hypertension, albuminuria, hematuria and cylindruria with increase in non-protein nitrogen of the blood and slight reduction of phthalein excretion. Rapid improvement. Refused tonsillectomy; persistence for one year of occasional edema of feet with mild albuminuria and cylindruria. Cultures from tonsils continue to show hemolytic streptococci of β type in considerable numbers.

Case VI. J. S., male, white, married, stevedore. Admitted to the Johns Hopkins Hospital January 2, 1926 complaining of swelling of ankles and face. No scarlatina, tonsillitis or diphtheria. Three years ago some swelling of body for two weeks. Two months ago swelling of feet gradually increasing to whole body; occasional cough and headache; vomited once. Examination showed anasarca with fluid in pleura and peritoneal cavities, edema of retina, enlargement of ton-

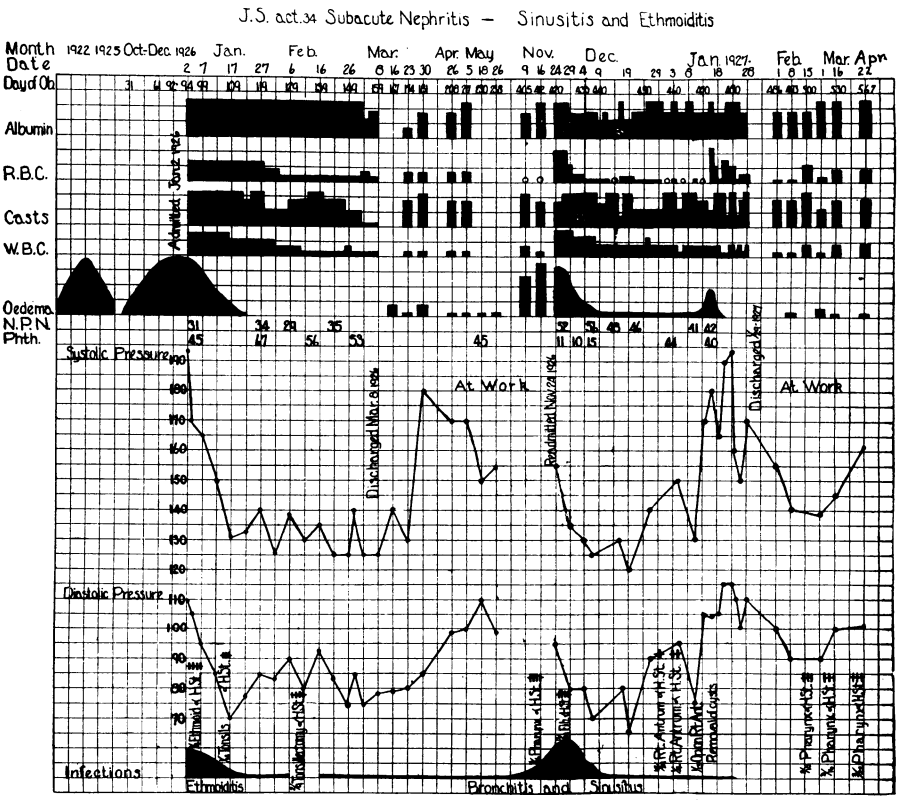

CHART VI. Case VI, showing the results of urine examinations, the changes in edema, the non-protein nitrogen of blood and phthalein excretion. the changes in blood pressure, the results of bacteriological examinations with course of infections charted chronologically.

sils, some widening of cardiac dulness. Point of maximum intensity 12 cm. to left in 5th space; heart sounds clear. Blood pressure 195/110. Muco-purulent discharge from ethmoidal regions. Temperature normal. Hemoglobin 62 per cent; red blood cells 3,160,000; white blood cells 9,800. Wassermann reaction negative. Cultures from ethmoidal regions give pure growth of streptococci of α type. Rapid improvement with disappearance of edema by January 26. Fundi

show perivasculitis and compression of veins by arteries. February 9 tonsillectomy. Discharged February 21 without edema. During next two months gradual return of edema, persistent moderate hypertension, marked albuminuria, cylindruria and occasional hematuria. Cultures from pharynx show great numbers of streptococci of α type. Readmitted November 24th with acute exacerbation of nephritis. There was pallor, anasarca, congestion and edema of nasopharnyx, few râles over left upper chest. Increased blood pressure (156/94), retinal edema and perivasculitis, albuminuria, hematuria, cylindruria. Hemoglobin 75 per cent; red blood cells 3,100,000; white blood cells 9,000; Phthalein 10 per cent. Cultures from pharynx show great numbers of streptococci of α type. Cultures from urine no growth. By January 6, 1927 there was great improvement with almost complete disappearance of edema, decrease in retinal perivasculitis and hematuria. X-ray showed polypi in right antrum. January 13, 1927 radical antrum operation by Dr. Crowe followed by recurrence of anasarca, increased hematuria and rise in blood pressure to 168/104. By January 28, 1927 much improved; condition practically the same as before operation. Since discharge has felt much better than for a year. Slight pretibial edema, some increase in blood pressure with albuminuria and cylindruria persisting. Cultures from pharynx have shown repeatedly streptococci of α type. Chart VI.

Summary: A case of subacute nephritis in a young man progressing to a chronic stage with repeated acute exacerbations. The exacerbations were accompanied by acute attacks of tonsillitis and sinusitis. Cultures from the nasopharynx showed streptococci of α type in great numbers during both the acute exacerbations and quiescent periods. Hypertension and increase of blood non-protein nitrogen, with decreased phthalein output during the acute attacks. Tonsillectomy with radical sinus operation one year later. Acute exacerbation of nephritis following latter operation with rapid improvement. Persistence of slight edema, albuminuria, cylindruria and hypertension, but general condition better than for a year.

Case VII. I. S., female, white, aet. 15, student. Admitted to Johns Hopkins Hospital December 13, 1926, complaining of swelling of face and ankles for one year. Measles and varicella. No scarlatina or diphtheria. Tonsillitis in 1922 followed by tonsillectomy. Otitis media two years ago. Colds with fever every winter. In November 1925 some swelling of ankles. In January 1926, face, eyelids and neck swelled and was told she had kidney trouble. Since June recurrent swellings of face accompanied by sore throat. Examination showed slight puffiness of face and edema of feet, pallor, reddening of pharynx, acute adenoiditis, systolic murmur at apex; blood pressure 136/84; edema of retina, albuminuria, hematuria and cylindruria. Hemoglobin 78 per cent, red blood

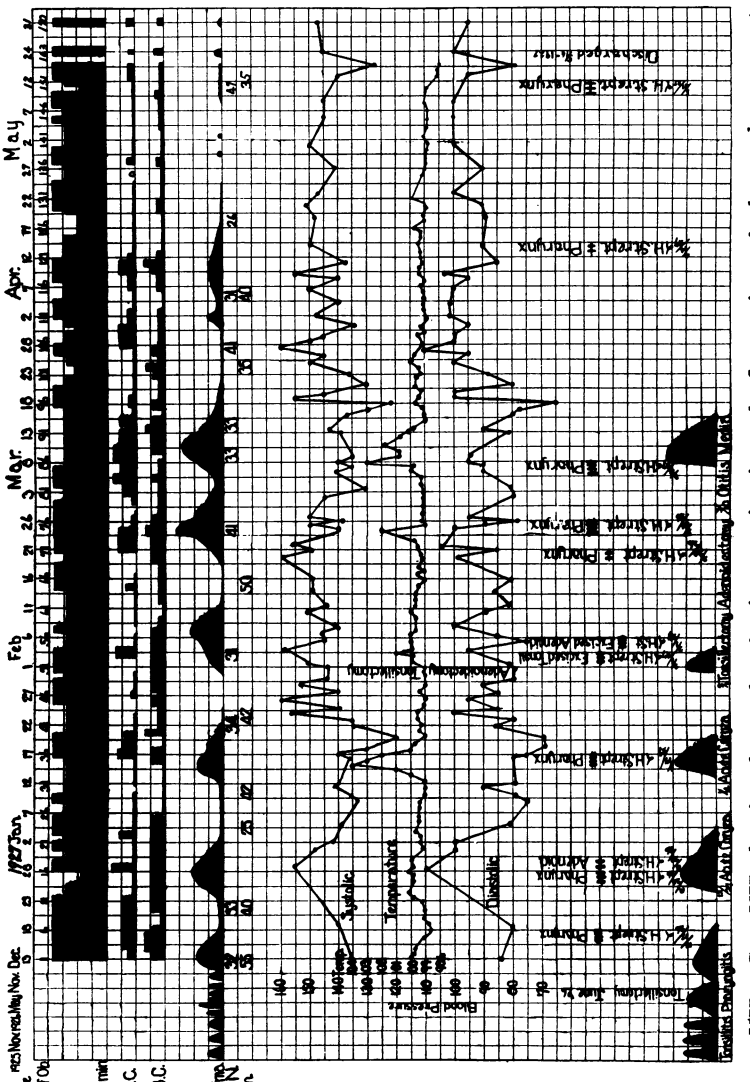

CHART VII. Case VII, showing the results of urine examinations, the fluctuations of edema, the non-protein nitrogen of blood and phthalein excretion, the changes in systolic and diastolic blood pressure, the temperature curve, the results of bacteriological examinations and the exacerbations of infection, charted chronologically.

cells 3,800,000; phthalein 55 per cent. Course in hospital characterized by many exacerbations of edema with increase in albuminuria and hematuria accompanied usually by fever, abdominal pain, leucocytosis of 13,000 to 17,000. One attack associated with acute otitis media and one attack with acute nasopharyngitis. Tonsillectomy and adenoidectomy. Cultures from excised adenoids and cultures made repeatedly from fauces and pharynx showed streptococci of α type in great numbers. Last seen Mary 31, 1927 and showed slight pretibial edema, some tortuosity of retinal vessels. Heart dulness 9.5 cm. to left in 5th space; blood pressure 146/100, albuminuria, hematuria, cylindruria. May 11 culture from pharynx gave streptococci of α type. Chart VII.

Summary: A case of nephritis in a young girl, progressing from a subacute to chronic stage with exacerbations accompanied by recurring infections of adenoids, nasopharynx and middle ear caused by streptococci of α type. Exacerbations of nephritis characterized by slight anasarca, fever, increased albuminuria, hematuria, cylindruria and gradual increase in blood pressure. Tonsillectomy and adenoidectomy. Persistence of streptococci of α type in almost pure cultures in pharynx.

The features which distinguish this second group of cases from the first are the persistence of definite evidence of renal injury for a long period as illustrated by case V, or the actual progression of the disease to chronic nephritis as illustrated by cases VI and VII combined with a persistence of the original infection or of the infecting organism. A close correlation between these two conditions occurred in 10 or 83.3 per cent of 12 cases. Of the two remaining cases, one after tonsillectomy continued a carrier of hemolytic streptococci of β type for a year, when these organisms disappeared from the pharynx. Later an infected antrum was drained. From the pus influenza bacilli and streptococci of α type were obtained. In the second of these two cases the acute attack of nephritis was accompanied by an acute tonsillitis due to hemolytic streptococci of β type. For a year after tonsillectomy cultures from the pharynx have not yielded hemolytic streptococci, but the patient has shown a persistent increase in blood pressure with some cardiac hypertrophy.

When one compares the natural history of the disease in these two groups, it becomes apparent that there is a relatively close correlation between the occurrence and persistence of infections caused usually by hemolytic streptococci with the onset and progress of the nephritis.

Though infections due to hemolytic streptococci precede or accompany the onset of a large proportion of all cases, complete recovery from the nephritis has rarely occurred unless the infection has been eliminated and the infecting organism has disappeared. Persistence or exacerbation of the infection with the continued presence of the organism has, on the other hand, been the rule in the cases that have progressed unfavorably.

It might be suggested that the difference in the course of the nephritis observed in these two groups depended in part or entirely upon the

TABLE 2

Bacteriology of infections occurring at onset of 34 cases of acute and subacute glomerular nephritis

Form of infection	Number of cases	Bacteria present					No predominating bacteria	No culture
		Strep. Hemolyt. β	*Strep. Hemolyt. α*	Pneumococci	*Staph. alb.*	Gonococci		
Tonsillitis	15	11	2				1	1
Tonsillitis and bronchitis	3	2					1	
Sinusitis	7	5	1	1				
Bronchitis, broncho-pneumonia, otitis and adenoiditis	4	2	1		1?			
Scarlet fever	4	2					1	1
Cystitis and pyelitis	1					1		
Total	34	22	4	1	1	1	3	2

. Of 32 cases cultured 22, or 68.7 per cent gave pure or predominating growth of hemolytic streptococci of β type and 4 or 12.2 per cent of α type.

severity of the initial acute attack of nephritis. It is probable that this has some bearing upon the rapidity with which convalescence may take place and may in occasional instances determine the ultimate recovery. But the attack of nephritis in some of the patients of the first group was quite severe, whereas the initial symptoms and the acute phase of the nephritis in some of the patients in the second group were rather mild; and it does not seem likely, therefore, that a variation in the severity of the onset could in itself be responsible for such pronounced differences in the subsequent course as occurred in these two groups of cases.

The frequency with which recrudescences have occurred during the progress of the nephritis has been noticeable both amongst those patients that have recovered and those who so far have not. In the majority of instances these exacerbations were related chronologically to mild or severe recurrences of the infection. In many instances the only evidence of an exacerbation of the nephritis was the sudden increase in albumin, red blood cells, casts, leucocytes and epithelial cells in the urine, with a change in character of the cells and casts; and it is readily conceivable that an individual might be the subject of repeated exacerbations of this character without knowledge of them. One is tempted to suggest that this is a common mode of progress from the acute to the chronic stage of glomerular nephritis.

Though the facts collected suggest that the streptococcus producing the infection in these cases is also the cause of the nephritis, it is not possible to obtain actual proof for this contention. There has been no evidence to show that the streptococci gained entrance to the blood stream, or that they were eliminated in these cases through the kidney, for blood cultures in the febrile periods were always negative, and cultures from the urine in amounts of 1 cc. to 5 cc. have never, except in one instance, shown a growth of the organism encountered in the infections of the upper respiratory tract or elsewhere. The exception occurred in the patient with cystitis in whom the infection was due to the gonococcus.

It has frequently been suggested that the toxic substances produced locally by the streptococci and eliminated through the kidney might be the cause of glomerular nephritis following scarlatina and tonsillitis, and it has seemed to us a much more probable explanation than that the bodies of the bacteria themselves transported to the kidneys set up an inflammation of the glomeruli. In order to determine whether the types of streptococci isolated from these infections might produce "toxic filtrates" similar to those derived from streptococcus scarlatina, the various strains were grown in peptone broth at a pH of 7.4 for 18 hours, the cultures filtered through Berkefeld "N" filters and 0.1 cc. of the diluted filtrate tested by intradermal injection in susceptible persons. An area of erythema exceeding 1 cm. in diameter and appearing after 18 to 24 hours was termed a positive reaction. Filtrates prepared in the above manner from 18 hour growths of

14 strains including both types of streptococci isolated from these infections have all produced skin reactions in 1 to 100 dilutions or 0.001 cc. Many have given positive reactions in 0.0005 cc. and 0.0001 cc. and a few in 0.00005 cc. or even 0.00002 cc.

It has been shown by Trask and Blake (1924) that the urine collected from cases of scarlet fever during the acute phase of the illness contains a "toxin" possessing the properties of the toxic filtrate from the growth of *Streptococcus scarlatinae*. Similar results have been obtained by Birkhaug (1927) with the urine from cases of erysipelas. Attempts have been made to demonstrate the presence of "toxins" in the urines of our patients. Intense skin reactions have often been obtained with such urines, but as albuminous urines from patients other than those suffering from acute nephritis or from streptococcus infections have produced similar reactions, it is obvious that until technical difficulties, occasioned probably by the presence of coagulable protein are overcome, it is impossible to draw any conclusion as to the cause of the skin reaction.

It is undoubtedly important to classify as accurately as possible the strains of streptococci isolated from these infections, in order to determine whether any of them correspond immunologically to the more or less fixed strains of hemolytic streptococci of β type. Work is now in progress upon this problem.

SUMMARY

1. The onset of acute or subacute glomerular nephritis in 40 patients was preceded or accompanied in 85 per cent by an acute infection such as tonsillitis, sinusitis, broncho-pneumonia or scarlatina.

2. Cultures made from the infections in 32 cases showed hemolytic streptococci of β type in 68.7 per cent, and streptococci of α type in 12.2 per cent.

3. Ten cases among those that could be constantly observed recovered apparently from the attack of acute nephritis. In 9 of these, or 90 per cent, the infection and the infecting organism have disappeared.

4. Twelve cases among those that could be constantly observed progressed to a chronic stage or terminated fatally. In 10 of these, or 83.3 per cent, the infection or the infecting organism has persisted.

5. No evidence could be obtained, in this study, to show that the streptococcus caused the glomerular nephritis by actual invasion of the kidney, for blood cultures and urine cultures were negative.

6. All the strains of the streptococci tested produced so-called "toxic filtrates," often of considerable potency and it seems possible that such "toxins" liberated by the growth of streptococci and eliminated through the kidney might cause glomerular nephritis in patients rendered highly susceptible in some way to these toxins.

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