Complement in Overt and Asymptomatic Nephritis after Skin Infection

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Abstract In an ongoing study of streptococcal skin infection and acute glomerulonephritis (AGN) begun in 1964, C'3 determinations were done in 784 patients. There were 126 patients with acute poststreptococcal nephritis, 172 of their siblings, and 486 patients with uncomplicated impetigo from families without an index case of nephritis.

90% of the patients with nephritis were infected with one of the four prevalent streptococcal serotypes associated with nephritis in this population; only 12% of patients with uncomplicated impetigo were infected with similar serotypes.

93% of the patients with overt nephritis had diminished complement levels. Low complement was more often observed (8%) in AGN siblings than was transient hypertension and/or hematuria (5%). Considering the relationship of low C'3 and hematuria, eight of the AGN siblings had low C'3 alone and low C'3 preceded hematuria in four others. Two (0.4%) of the patients with uncomplicated impetigo had low complement values, both of whom were infected with nephritogenic strains. Transient hematuria and/or hypertension was less frequently observed (2.7%) among patients with uncomplicated impetigo. Serial determinations in patients with low complement revealed a return to normal in a linear fashion within 2–12 wk.

The validity of the hypothesis that the asymptomatic patients with low complement levels, with or without hematuria, likely had subclinical nephritis is strengthened by the accompanying epidemiologic data. The finding of low complement before the onset of, or in the absence of, hematuria or other evidence of nephritis supports the concept that an immunologic mechanism may precipitate the renal injury of acute streptococcal nephritis.

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INTRODUCTION

Since Bright's classical description of nephritis in 1836 (1), physicians over the years have come to recognize the self-limited illness of childhood manifested primarily by abrupt onset of edema, hypertension, and hematuria to be typical of poststreptococcal acute glomerulonephritis. Early epidemiologic studies revealed that nephritis could follow antecedent infection of either the skin and soft tissues or the respiratory tract (2). As epidemiologic studies of nephritis further evolved it became apparent that most cases followed infection with limited serotypes of streptococci, leading to the concept of there being nephritogenic strains of streptococci (3). This concept helped to explain the high attack rates of nephritis seen when epidemic infection with certain serotypes occurred and the tendency for multiple cases of nephritis to occur within a short period of time within families infected with nephritogenic strains (4–6).

The variability in the clinical expression of acute nephritis has been previously recognized. Hematuria has been found to occur more often in the absence of other evidence of nephritis in those patients infected with a recognized epidemic nephritogenic strain (5). In the most recent outbreak of nephritis at Red Lake, Minn., where type 49 streptococci were again incriminated, fully half of the cases were subclinical, having only microscopic hematuria and being ultimately documented by renal biopsy (7, 8). Recently cases of nephritis based on histopathologic evidence have been described in which urine abnormalities were absent (9–12).

With the advent of complement studies in renal disease an additional diagnostic test for nephritis became available (13). It is now well established that the glycoprotein C'3 (B_1C/B_1A-globulin), the third component of serum complement, is low in the initial stage of acute

poststreptococcal glomerulonephritis (14–16). In contrast to other forms of nephritis in which the complement level may be either normal or persistently decreased, complement levels are sharply decreased in the acute phase of poststreptococcal nephritis but return to normal within a few weeks (17, 18). C'3 determinations thus provide a simple and useful means of further defining suspected cases of acute nephritis.

During the past 5 yr an extensive study of the epidemiology of nephritis associated with skin infection has been in progress. Patients with typical overt nephritis have routinely been found to have low C'3 levels early in the course of their illness. The return of C'3 to normal has paralleled both clinical recovery and the return of other laboratory abnormalities such as hematuria to normal levels. Recently simplification of the technique for determining B_1C/B_1A-globulin has provided the means for rapid serial determinations in patients with skin infection admitted to the prospective study. As a result, it has been found that in some children infected with a recognized nephritogenic strain of streptococcus, low levels of B_1C/B_1A-globulin appear to be the earliest or only evidence indicative of nephritis. The data suggests that these children have subclinical poststreptococcal nephritis and supports the concept that an immunologic mechanism precipitates the renal injury. C'3 determinations in sibling contacts of children with overt nephritis or others infected with a recognized nephritogenic strain appear to be an important means of determining the spectrum and incidence of nephritis associated with streptococcal infection.

METHODS

Clinical methods

A prospective study of streptococcal skin infection and acute glomerulonephritis was initiated in July of 1964. The details of patient selection and methods of examination employed in the continuing prospective studies have been previously described (19, 20). The clinical categories in which patients are shown in this report, also separately described (19), include the following groups: uncomplicated impetigo; overt (symptomatic) acute glomerulonephritis, referred to hereafter as overt AGN; and siblings of patients with acute glomerulonephritis, subsequently referred to as AGN siblings. Patients with uncomplicated impetigo include children with skin infection, without AGN present in either the patient of family contacts. Children with overt AGN include only patients with symptomatic illness characterized by an acute or abrupt onset, all of whom were hospitalized. The major clinical and laboratory manifestations, other than C'3 data, of the latter patients are shown in Table I. None of the children with acute nephritis had prior evidence of renal disease. Clinical features not shown in the table but occasionally seen included congestive heart failure and encephalopathy. Chest X-rays obtained on admission to the hospital revealed some evidence of pulmonary edema and/or cardiac enlargement in over half the children with overt AGN. The clinical severity of nephritis varied widely but the average hospital stay of these patients was 10 days.

TABLE I

Clinical and Laboratory Features of Overt AGN in 126 Patients

Clinical features	% Frequency	Laboratory features	% Frequency
Hypertension	97	Streptococcal infection	±100
Edema*	90	Hematuria	100
Oliguria*	88	Cylinduria	82
Dark Urine	32	Proteinuria	90
		Elevated ESR	92
		Elevated BUN and/or creatinine	47 ...

± Based on recovery of group A streptococci and/or elevated streptococcal antibody titer.

* Based on clinical findings, diuresis, and weight loss.

TABLE II

Clinical Categories and Number of Patients with C'3 Determinations

Study periods	Overt AGN	AGN siblings	Uncomplicated impetigo	Totals
1964–67	100	100	230	430
1968	26	72	255	353

AGN siblings were examined as soon as possible, usually within 1 wk, after recognition of the index case of nephritis within the family. Screening examinations were done in all siblings whether or not evidence of streptococcal skin infection was found.

The age range of patients being reported was from 8 months to 18 yr with a mean of 6.6 yr. 85% of the patients were Negro, with an equal number of males and females being seen in patients without nephritis. There was a 60 to 40 male to female predominance among the children with nephritis.

Laboratory methods

Bacteriology. Cultures were obtained and processed as previously described (19). All group A streptococci were serotyped in this laboratory by both agglutination (21) and precipitin (22) methods. Reference sera used were from National Communicable Disease Center, Atlanta, Ga., and Public Health Reference Laboratory, Colindale, London (courtesy of Dr. M. T. Parker and Dr. W. R. Maxted). Representative strains were also serotyped at the latter two reference laboratories (19). In addition to standard reference sera, sera for provisional new types have been employed, including those prepared at NCDC, at Colindale, and in this laboratory.

Serology. Anti-streptolysin O and anti-DNAse B determinations have been performed on patients reported in this study (23).[1] Elevation of either or both titers was considered serologic proof of streptococcal infection.

Urinalyses. Freshly voided urine specimens were examined in the clinic using commercially available test strips

[1] Manuscript in preparation.

TABLE III

Antibody Titers in Streptococcal Skin Infection

Patients	Elevated titers	
	A-DNAse B	ASO
	%	
AGN	92	51
Siblings of AGN	72	21
Other impetigo	67	43

(Hema-Combistix, The Ames Co., Elkhart, Ind.). The determination of occult blood by this method has been found by us as well as others (8, 18, 24) to be a highly sensitive test especially for hemolyzed red cells. Positive tests for occult blood determinations by this method were rated as "small," "moderate," or "large." Proteinuria, also tested with the same test strip, was graded trace to 4+. In patients seen before the 1968 study, microscopic examinations of urine were done in all cases. In 1968, microscopic examinations were routinely done only on urine specimens found to be positive for hematuria by the test strip method.

C'3 determinations. C'3 (B_1C/B_1A-globulin) was determined semiquantitatively by the immunoelectrophoretic method of Scheidegger (25) on the sera obtained during the 1964–67 periods of study. The B_1C/B_1A bands were read as "normal," "significant decrease," and "trace" or "absent." A standard control was run with each preparation. Serial determinations were routinely done only in children with evidence of acute nephritis. A limited number of serial determinations were done in patients in the other clinical categories. In 1968, C'3 determinations were quantitatively determined by the radial immunodiffusion method (26) using commercially prepared immunodiffusion plates (Hyland-Human Complement C'3 Test). Duplicate determinations were routinely done on separate plates for sera with either low or elevated values. The C'3 values obtained by this method were consistently reproducible. Three or more determinations were done on fresh sera on all 353 patients. The number of patients in whom C'3 determinations were done during each of the periods of study being reported is shown according to clinical category in Table II. Quantitative determinations were done in a control population, drawn from the outpatient clinic in which studies were being done, and consisted of 56 children free of evidence of streptococcal and/or renal disease. These children were similar with regard to race, age, and sex distribution, to the patients admitted to the prospective study.

RESULTS

Serologic evidence for streptococcal infection. The anti-DNAse B test has been found most useful in documenting a serologic response to streptococcal skin infection (23). As shown in Table III, titers were elevated in over 90% of patients with overt AGN. Antistreptolysin (ASO) titers were significantly less often elevated in both the patients with AGN and those in the other two patient groups.

Nephritogenic streptococci. The major nephritogenic strains of streptococci in our population over the past 5 yr have been M-types 2 and 49 (27) followed by two other provisional new types, 59 and 60, identified in this laboratory.[2] They are referred to herein as "D-13" and "Alabama-4." The prevalence of these various strains is summarized in Table IV. Their relation to clinical and subclinical cases of AGN is given in more detail in following sections of this report.

1964–1967 study. Results of B_1C/B_1A-globulin determinations, done by the immunoelectrophoretic method, in patients studied before 1968 are shown in Table V. As expected, the majority (92%) of patients with overt AGN had markedly decreased levels; in 51% no C'3 was detected by this method. 74 of the 100 AGN siblings studied, including those five with low C'3, were seen in 1967. The latter five patients were each infected with one of the common nephritogenic strains in this population (types 2, 49, or "Alabama-4"). Hematuria occurred in only two of the five patients, in both cases after the C'3 was found to be low. One of the two subsequently developed clinically overt evidence of AGN. In the remaining three patients, the low C'3 was the only evidence suggestive of AGN. Hematuria occurred as an isolated finding in 2 of the 95 siblings with normal C'3 levels. In neither case did other evidence of AGN develop.

Among the group of 231 children with uncomplicated impetigo, 145 of whom were examined in 1967, only 1 patient had a significant decrease in C'3. This particular patient was one of only three in the uncomplicated impetigo group to be infected with an M-type 2 streptococcus which, together with type 49, accounted for most cases of AGN that year (27). She remained free of hematuria and clinical evidence of AGN, and the low C'3 level returned to normal within 14 days.

Thus, a total of six patients, other than those with overt AGN, were found to have low C'3 levels during

[2] Manuscript in preparation.

TABLE IV

Serotypes of Streptococci in Patients with and without Nephritis

Streptococcal serotypes	Clinical category*	
	AGN	Uncomplicated impetigo
	%	
M-type 2	43	1
M-type 49	30	6
"Ala-4" (prov. type 60)	10	2
"D-13" (prov. type 59)	7	3

* These figures are based on a total of 146 initial skin isolates from patients with AGN and 1327 initial skin isolates from patients with impetigo, in families without evidence of AGN.

TABLE V

Results of C'3 Determinations in Patients Studied in 1964–67*

Patient category	No.	Normal C'3	Significantly reduced or absent C'3
AGN	100	8	92
AGN siblings	100	95	5
Impetigo	231	230	1

* Determined by immunoelectrophoresis.

the 1964–1967 period. All 6 were infected with a nephritogenic strain common in this population. Hematuria was detected in only two of these patients, in both cases after C'3 was observed to be low, and only one of these children progressed to develop overt AGN.

Hematuria occurred in only 3 of the 230 patients with impetigo and normal C'3 levels. These children had no other evidence of AGN and were not infected with strains commonly associated with nephritis in this population.

1968 study. During 1968 there were 26 patients with overt AGN, 69% of whom were infected with either M-2 or M-49 strains. Type 2 was predominant. 53 of the 72 AGN siblings had skin infection, 72% of whom were infected with one of these two M-types. In marked contrast, only 4.5% of the 255 uncomplicated impetigo patients were infected with either type 2 or type 49 streptococci.

Hematuria and proteinuria were present in varying degrees in all overt AGN patients; hematuria persisted up to 3–4 months in some cases. Hematuria, varying from small to moderate in amount, was found in seven of the uncomplicated impetigo patients (less than 3%). The hematuria was detected on one visit only in 6/7 of the patients and on two separate occasions in the other patient. Hematuria detected in six of the 72 AGN siblings (8%) was found on two or more occasions in four patients and only once in the other two. The degree of hematuria, as determined by the Hemastix method, varied from small to strong reactions. Proteinuria in trace to 1 + amounts was transiently present in 15 of the uncomplicated impetigo patients and in 4 of the AGN siblings.

As stated earlier, in 1968 C'3 was quantitatively determined by the immunodiffusion method. The reported normal value in adults[3] is 145 mg/100 ml ±SD 22 mg/100 ml. The lower limit of normal for this population as determined in the control group is 100 mg/100 ml (mean less 2 SD). This figure is similar to that reported by West, McAdams, McConville, Davis, and Holland (17) and more recently by Gotoff, Isaacs, Muehrcke, and Smith (16).

Results of the C'3 determinations are shown in Fig. 1. The mean value of the control group was 204 mg/100 ml. Individual patient determinations have been plotted and the mean values for the various groups are depicted in the left margins.

[3] Hyland-Human Complement C'3 Test.

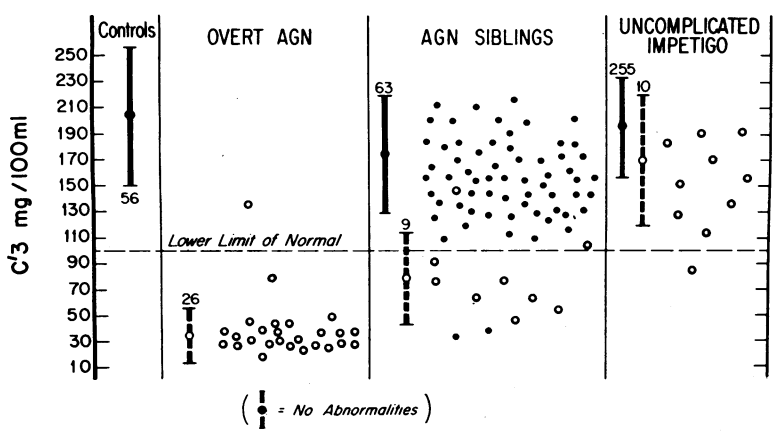

FIGURE 1 C'3 determinations in patients with skin infection and AGN. C'3 determinations in a control population and the various study groups are shown in the left margins as the mean ±1 SD. Means were determined separately for those children with uncomplicated impetigo and those AGN siblings who were found to have hematuria and/or hypertension. Individual determinations are shown for the overt AGN and AGN sibling groups and for the 10 patients in the uncomplicated impetigo group with abnormal findings. Open circles represent patients with overt AGN and those in the other groups with hematuria and/or hypertension. Patients without these abnormal findings are represented by closed circles.

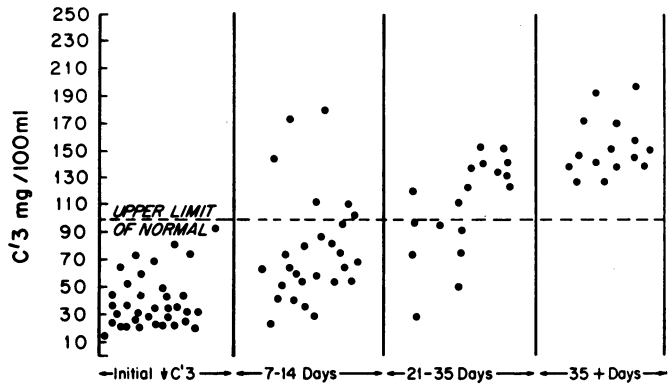

FIGURE 2 Duration of low C'3 levels in the various patients with clinical and subclinical AGN. 24/35 patients with a low C'3 level were followed serially until C'3 returned to normal.

Considering first the C'3 values in the overt AGN patients (mean = 37 mg/100 ml), all but one fell well below the lower limit of normal. The one exception was a patient seen too late in the course of nephritis to permit a valid evaluation of C'3. For comparison, the AGN siblings with and without evidence of hematuria and/or hypertension are depicted in the second portion of the figure. The mean level in the 63 AGN siblings without abnormal findings (177 mg/100 ml) was not significantly different from that of the control and uncomplicated impetigo groups. However, the mean C'3 in the AGN siblings with transient hematuria and/or hypertension was 77 mg/100 ml, a value well below the lower limit of normal ($P < 0.001$) and considerably nearer the mean found for the 26 overt AGN patients. Seven of the siblings with hematuria and/or transiently increased blood pressure had a low C'3 and one other was borderline (102 mg/100 ml). 2 of the 63 siblings without these abnormalities also had a low C'3, making a total of 9 AGN siblings with levels less than normal. Patients in the uncomplicated impetigo group had a mean level of 197 mg/100 ml, almost identical with the controls. Individual values are shown only for the 10 patients in this group who had transient hematuria and/or hypertension. The mean of 170 mg/100 ml for these patients was not significantly different from that in the patients without hematuria or hypertension. Of these 10 patients, only 1 had a low C'3. He was the only 1 of the 10 from whom a recognized nephritogenic strain was isolated. None of the remaining 245 uncomplicated impetigo patients without abnormal findings had levels lower than those shown for these 10 patients. The occasional high values obtained in the various patient groups were considered to represent an acute phase reactant.

Assessment of the duration of hypocomplementemia was limited since the initial determination was low in most patients with low values. However, the time interval graph, depicted in Fig. 2, which illustrates initial and all subsequent C'3 values, demonstrates that C'3 returns to normal in a linear fashion. 24 of 35 patients with low C'3 determinations were examined serially until their complement returned to normal. 15 were followed at 1- to 2-wk intervals. Of these 15 patients, 5 had normal values within 7–14 days, 7 within 21–35 days, and 3 others after 35 or more days. The average duration of low C'3 levels in these 15 patients was 25.1 days. The other nine patients with low C'3 were found to have normal levels when retested 2–4 months later.

Hematuria, transient hypertension, and low C'3, occurring singly or in varying combinations, have been considered as suggestive evidence of subclinical AGN. These findings along with the serotype of infecting streptococcus are correlated for children studied during 1967–68 in Table VI. There were 15 AGN siblings (VI *a*) and 14 children with uncomplicated impetigo (VI *b*).

All but one of the AGN siblings were infected with a strain of recognized M-serotype commonly associated with nephritis in this population. The exception was a child with a strain identified by agglutination only as T-12. (M-type 12 and 22 are both known to carry this antigen.) In contrast, among those patients with uncomplicated impetigo a smaller percentage of strains were typable with available M antisera, including that prepared against provisional new serotypes. Agglutination patterns identified among these impetigo isolates, the most common of which was 3/13/B3264, are those recognized to be characteristic of impetigo streptococci wherever they are encountered. Several M-types, M-33, 39, 41, 43, 52, and 53, share this complex and none of these have been prevalent in our population.

The striking finding in the AGN sibling group of 15 children was the demonstration of low C'3 in 13 of them whether or not other abnormalities were found. The low

TABLE VI

Correlation of Factors Suggestive of Subclinical AGN in Asymptomatic Patients

Patient	Streptococcal serotypes			C'3	Occurrence and frequency*	
	T-Agglutination	M-Precip.	Nephritogenic strains		Hematuria	Hyper-tension
a AGN sibling						
V. W.	8/25/Imp. 19	M-2	+	↓	++	+
S. W.	8/25/Imp. 19	M-2	+	↓	++	0
R. C.	8/25/Imp. 19	M-2	+	↓	++	0
M. B.	8/25/Imp. 19	M-2	+	↓	+++++	0
P. M.	8/25/Imp. 19	M-2	+	↓	0	+
Z. B.	49	M-49	+	↓	0	+
L. C.	8/25/Imp. 19	M-2	+	↓	0	0
S. A.	8/25/Imp. 19	M-2	+	↓	0	0
P. B.	8/25/Imp. 19	M-2	+	Normal	+	+++
B. F.	12	M-neg.	0	Normal	+	+
P. C.	8/25/Imp. 19	M-2	+	↓	0	+
Z. H.	49	M-49	+	↓	0	0
E. J.	8/25/Imp. 19	M-2	+	↓	0	0
D. C.	4	"Ala-4" (Prov. 60)	+	↓	+	0
H. W.	4	"Ala-4" (Prov. 60)	+	↓	0	0
		Totals	14	↓13	7	6
b Uncomplicated impetigo						
T. B.	"D-13"	"D-13" (Prov. 59)	+	↓	+	+
S. E.	8/25/Imp. 19	M-neg.	0	Normal	+	+
A. L.	3/13/B	M-neg.	0	Normal	0	+++
E. H.	3/13/B	M-neg.	0	Normal	0	++
B. H.	12	M-neg.	0	Normal	0	++
T. M.	5/12/27/44	M-neg.	0	Normal	+	0
J. B.	3/13/B	M-neg.	0	Normal	+	0
C. L.	"D-13"	"D-13" (Prov. 59)	+	Normal	++	0
K. W.	3/13/B	M-neg.	0	Normal	+	0
L. T.	8/25/Imp. 19	M-neg.	0	Normal	+	0
S. T.	8/25/Imp. 19	M-2	+	↓	0	0
W. M.	14/Imp. 19	M-neg.	0	Normal	+++	0
M. H.	8/25/Imp. 19	M-8	0	Normal	+	0
R. W.	14/Imp. 19	M-neg.	0	Normal	+	0
		Totals	3	↓2	10	5

* Number of +'s = number of times documented.

C'3 occurred in the absence of hematuria in eight of these children and was observed to precede the occurrence of hematuria in four others. In all, hematuria occurred in only 7 of the 15 siblings, 4 of whom had documented hematuria on more than one occasion. Two of those siblings with hematuria represented the two children from this group with normal complement levels. Asymptomatic hypertension was the only abnormal physical finding detected in this group of patients, occurring transiently in six of them. Two of the six had normal C'3. The combination of low C'3, hematuria, and transient hypertension occurred in only 1 of the 15 siblings.

In examining the data obtained from those children with uncomplicated impetigo (VI *b*), it is apparent that few of these children were infected with nephritogenic streptococci. However, the two patients in whom C'3 was low were both infected with strains associated with nephritis. The contrast in this group of patients and the AGN siblings is further apparent when it is seen that

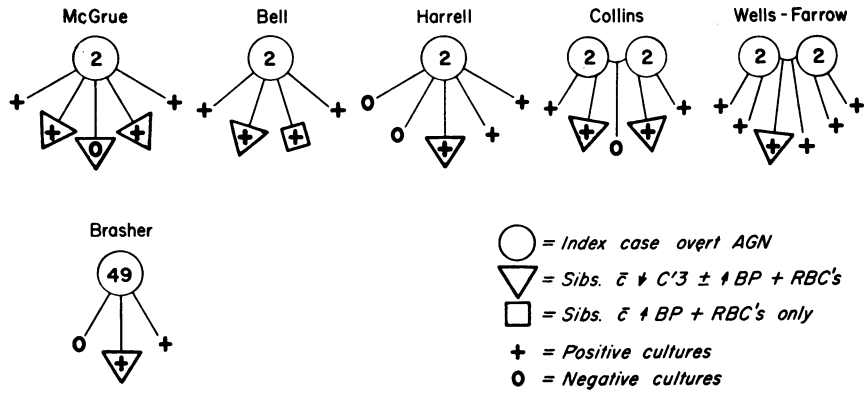

FIGURE 3 Subclinical nephritis in relation to serotype and index case (1968 study). The high attack rate of nephritis in families infected with nephritogenic strains, notably type 2, is shown. 17 of the 36 patients from these 6 families had either overt or subclinical AGN, representing an attack rate of 47%.

although hematuria was observed in 10 children, C'3 was normal in 9 of the 10 cases. Asymptomatic hypertension occurring transiently in five of these children was an isolated finding in three patients; only one patient (T.B.) was observed to have a low C'3 with hematuria and hypertension. The significance of transient asymptomatic hypertension in these patients is uncertain.

Considering evidence in support of the diagnosis of subclinical nephritis in these various patients, low C'3 values in siblings of children with nephritis, who themselves are infected with nephritogenic strains, was the most consistent and striking abnormality observed. The fact that low C'3 occurred in the absence of hematuria in some cases and preceded hematuria in additional cases is in keeping with the concept that complement utilization in an immunologic reaction precedes renal injury in AGN.

Multiple cases of clinically overt AGN, or examples of overt AGN and suspected subclinical AGN within a given family, were commonly observed. These "family clusters" from the 1968 study are shown in Fig. 3. The nine AGN siblings with low C'3 levels are shown in relation to their siblings with overt AGN, and streptococcal serotyping data are given. The nine AGN siblings were from six family groups; M-type 2 streptococci were found in five families, and M-type 49 in one. A total of 36 patients were represented in these six families. 17 of them had either overt (8 patients) or subclinical (9 patients) evidence of nephritis. This represents an attack rate of 47% in these six families in whom infection with one of the two prevalent strains of nephritogenic streptococci found in our population occurred.

DISCUSSION

The diagnostic value of C'3 determinations in acute poststreptococcal glomerulonephritis is unquestionable. In the experience reported here, both methods of determining B_1C/B_1A-globulin proved acceptable. The quantitative method (radial imunodiffusion), however, was shown to have several advantages: it is done with little equipment and results are clearly reproducible; results are expressed in terms permitting mathematical comparison between patients and groups of patients and statistical analyses; the simplicity of the method lends itself to rapid screening of large numbers of sera (24).

In those patients with typical findings of acute glomerulonephritis, herein called overt AGN, C'3 was markedly reduced as expected early in the course of the illness. Reduced levels of C'3 often persisted beyond the acute phase of the disease but the trend, as shown by serial determinations, was toward a gradual return to normal within a few weeks. These findings serve to further differentiate poststreptococcal nephritis from those nephritides in which C'3 remains normal or is persistently low (13–18, 28).

The validity of the hypothesis presented here that asymptomatic patients with low C'3 levels, with or without hematuria, had subclinical nephritis is strengthened by accompanying epidemiologic data. Streptococcal M-types 2 and 49 have been documented as the major serotypes associated with skin infection and nephritis in this population (27). Three provisional new types, recently identified in this laboratory, have also been incriminated in nephritis;[4] at least one of which ("Alabama-4," provisional type 60) appears to be of importance as a cause of nephritis in Trinidad.[5] Neither types 2 and 49, nor the new serotypes, have been often seen other than in families in which one or more overt cases of nephritis have occurred. With only two exceptions, the subclinical cases occurred in families in which one or

[4] Manuscript in preparation.
[5] Personal communication.

more siblings infected with an identical serotype had classical acute nephritis. In every case, patients with subclinical nephritis themselves were infected with a recognized nephritogenic strain. The streptococcal epidemiologic data are also of significance in evaluating hematuria in patients defined herein as having uncomplicated impetigo. A relatively low incidence of hematuria was observed in that large group of children. Although the question of streptococcal infection and hematuria will not be reviewed in depth, it is pertinent to examine certain data on this subject. Investigators have sought to distinguish hematuria related to streptococcal-induced renal injury from that which may be coincidental or perhaps occurs as a manifestation of nonspecific infection. Stetson, Rammelkamp, Krause, Kohen, and Perry were the first to clearly demonstrate a relation between the incidence of and degree of hematuria and the serotype of infecting streptococcus (5). Their observations came during the now-classic studies of epidemic nephritis associated with M-type 12 streptococci. Transient hematuria occurred more often in patients with type 12 streptococcal infection than in those infected with other serotypes; furthermore, overt nephritis developed more often in the former patients with this early, transient hematuria.

The recent reports of Anthony and coworkers of studies of skin infection among Indian children at Red Lake Indian Reservation in Minnesota are of particular interest (7, 8, 29). The original epidemic of nephritis, due to type 49 streptococcal skin infection, occurred at that reservation in 1953 (30, 31). Prospective studies of skin infection were instituted there in 1964, and though a high seasonal incidence of streptococcal pyoderma was demonstrated, very little hematuria or nephritis was seen until 1966. During that year, type 49 reappeared and caused a second epidemic of nephritis. 21 patients were diagnosed as having either clinical or subclinical AGN by renal biopsy. In addition, hematuria was prevalent in other children in the prospective study infected with type 49. The hematuria in those children has been recently described as "unexplained," since no other confirmation of nephritis was obtained (8). No serum complement data were reported. The incidence of hematuria was clearly greater in children with recognized type 49 infection than in those children reported earlier with a variety of serotypes of streptococci, none of which could be clearly related to nephritis. Recently patients with nephritis have been described in which urine findings were either atypical, minimal, or absent (9–12). These cases were suspected on clinical grounds and include examples of nephritis well documented by histopathologic studies. Serum complement studies, however, were not reported for these various patients.

Kidney biopsy is not feasible in all patients in whom the diagnosis of acute glomerulonephritis may be suspected on either clinical grounds or because of the finding of abnormalities in the urine. Our own experience would indicate that serial complement studies can be of great value in confirming the clinically obvious case and in supporting the diagnosis of subclinical nephritis or probable nephritis in patients infected with nephritogenic streptococci whether or not urine abnormalities are present.

The prevailing concepts of the pathogenesis of poststreptococcal nephritis have arisen from studies of immune complex nephritis in experimental animal models and studies of renal tissue of patients with nephritis (32, 33). Immunopathologic studies have demonstrated the deposition of products including immunoglobulins, fibrin, and complement in the glomeruli of patients with poststreptococcal AGN (34–39). However, streptococcal products have been demonstrated in only limited instances (34, 36, 39). A form of nephritis similar to that seen in man has now been produced in rabbits with nephritogenic strains of streptococci (40). The histopathologic changes in that model are strikingly like those seen in man.

Our findings that C'3 values were low before onset of hematuria or other evidence of nephritis in some cases strongly supports the concept that C'3 participates in an immunologic reaction that injures the kidney before subsequent evidence of renal disease becomes apparent. The mean C'3 in those patients with overt nephritis was somewhat lower than that mean in children defined here as having subclinical nephritis. The relation between the degree of the suppression of complement and clinical severity of nephritis remains uncertain. The evidence is now questionable from other studies as to whether or not clinical severity of nephritis, urine abnormalities, and histopathologic changes can be clearly correlated. Among the cases described here were those children in whom the only evidence of subclinical nephritis was a low C'3. The sensitivity of the methods of detection used in these patients make it unlikely that significant hematuria was missed. In the absence of kidney biopsy the question might be posed as to whether the term "subclinical nephritis" should be employed. The natural history of poststreptococcal nephritis in children is such, however, that it seems difficult to justify kidney biopsies in such individuals. Rather, it seems appropriate that children suspected or known to have infection with nephritogenic strains of streptococci can be followed in the manner described here, and serial C'3 determinations can be relied upon as a sensitive laboratory indicator of this poststreptococcal complication.

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