HYPERLIPEMIA IN EARLY STAGES OF ACUTE GLOMERULAR NEPHRITIS *

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Marked hyperlipemia, involving all lipid fractions, is a regularly noted observation in the nephrotic syndrome (1). In contradistinction, the serum lipid concentration is believed to be almost unaffected in early stages of acute glomerular nephritis, even though one can find data in the literature that indicate that increased concentrations of serum cholesterol may rarely be noted (1–5). As a consequence of continued interest in the pathogenesis of the nephrotic hyperlipemia (6) we have, during the past 10 years, obtained data on serum protein and/or albumin, cholesterol and /or total lipid concentration in 111 unselected cases of acute glomerular nephritis. The results of these studies will be presented and discussed in this communication. They indicate that the aforementioned contention can no longer be accepted without modification.

METHODS AND MATERIAL

Serum protein and albumin were determined according to the method of Weichselbaum (7). For the determination of total lipids and cholesterol in serum, the methods of Wilson and Hanner (8), and Schoenheimer and Sperry (9), respectively, were used. All samples were obtained after an overnight fast.

From 1948 to 1957, 248 children suffering from acute glomerular nephritis were admitted to Babies and Children's Hospital. The diagnosis was made on the basis of a preceding history of infection, the finding of proteinuria with hematuria, with or without fever, edema, hypertension and azotemia, and a benign course of the disease ending in cure. In 111 of these, chemical data were obtained which provide the material for our report. By chance, not by selection, neither cholesterol nor total lipid values were obtained at any time in the remaining 138 patients. No indication to obtain serum protein and lipid values prevailed except a well established diagnosis of acute glomerular nephritis, regardless of severity.

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Nose and throat cultures were obtained in all but 11, and 31 of these yielded beta hemolytic streptococci. Three of these were typed [1] and were of the nephritogenic Type 12. Antistreptolysin "O" titers were obtained in 36 children. Thirty-one of these were greater than 333, the remaining five varied between 166 and 250. Forty-six children were re-examined more than four weeks after onset. Twenty-five of these were seen two to eight years after onset of the acute disorder. Urine examinations were negative in all. None of the remaining 65 children has been re-admitted with a relapse or with chronic renal disease. The age distribution of these 111 patients is charted in Table I. It is in agreement with previously established (1, 10) figures in that 75 per cent of the patients were older than four years of age, whereas in the nephrotic syndrome of unknown etiology the majority of the children are less than four years of age.

One hundred twenty-three children, 1 to 15 years of age, in whom either cholesterol, total lipids and/or serum protein and albumin values had been obtained, served as controls. Of these, 98 were free of infections. They had been admitted because of psychiatric, neurologic, allergic, orthopedic or ophthalmologic problems. In the 25 additional children of this group, blood was obtained during a febrile episode in 14, and 1 to 12 days after fever had subsided in 11. One of these patients had typhoid fever, two were febrile with rheumatoid arthritis and the re-

TABLE I

Age distribution of 111 children with acute glomerular nephritis

Age in years	No. of cases	Per cent
1	0	0
2	7	6.4
3	11	9.9
4	10	9.0
5	20	18.0
6	19	17.1
7	17	15.3
8	10	9.0
9	5	4.5
10	7	6.3
11	2	1.8
12	2	1.8
13	1	0.9

[1] We are indebted to Dr. Floyd W. Denny from the Departments of Preventive Medicine and Pediatrics for carrying out the typing.

TABLE II

Distribution of serum protein and serum albumin values in children with acute glomerular nephritis and controls (with and without infections)*

	Acute glomerular nephritis		Controls			
			With infections		Without infections	
	No. of cases	Per cent	No. of cases	Per cent	No. of cases	Per cent
Serum protein Range of values	50		16		42	
Gm. %						
8–9	1	2	3	19	8	19
7–8	5	10	4	25	21	50
6–7	21	42	6	37	10	24
5–6	12	24	3	19	3	7
4–5	11	22	0	0	0	0
Serum albumin Range of values	34		16		37	
Gm. %						
5–6	1	3	0	0	21	57
4–5	9	26	12	75	13	35
3–4	16	47	3	19	3	8
2–3	7	21	1†	6	0	0
1–2	1	3	0	0	0	0

* First values obtained 6 to 24 days after onset of disease.
† Two and one-half year old male, typhoid fever. Value of 2.6 Gm. % obtained after three weeks of fever and poor intake of food.

maining 23 had upper respiratory infections of viral or bacterial origin. All were free of renal complications, in good state of nutrition, with the exception of the two and one-half year old patient with typhoid fever indicated in Table II.

RESULTS

Serum protein values were obtained in 50 and serum albumin values in 34 cases of acute glomerular nephritis. The first value, obtained 6 to 24 days after onset of the disease, is presented in Table II. These values can be compared with corresponding values obtained in 58 controls, 16 of whom had, or recently had had, one of the quoted infections. It can be seen that serum protein and albumin values below lowest values obtained in the controls were noted in over 20 per cent of the children with glomerular nephritis. More than one determination was obtained in 16 of these children. Figure 1 represents all values obtained in this group of children, and relates these values on the abscissa to the onset of the disease. It can be seen that hypoproteinemia and hypoalbuminemia were most marked 2 to 15 days after onset and persisted as long as 23 days after first symptoms of nephritis were observed.

Values for serum total lipids were obtained in 37 children with acute glomerular nephritis and 32 controls. Of the control subjects, 25 were free of any detectable infections, whereas seven had, or recently had suffered, a febrile illness. Table III shows that 43 per cent of the patients suffering from acute nephritis had on first measurement, 6 to 24 days after onset of the disease, higher total lipid values than were ever obtained in control subjects. A similar figure of 40 per cent is obtained from Table III as far as serum cholesterol concentration in the nephritic group of children is concerned. The statistical evaluation of these results yielded for total lipids as well as for cholesterol a value for p of < 0.01. More than one determination was obtained in 21 of these children. Figure 2 represents all values obtained in this group of children and relates the serum lipid and cholesterol concentration (ordinate) to the onset of the disease (abscissa). It may be seen that total lipid values may be increased as early as two days and cholesterol concentration as early as four days after onset. Highest values were obtained one to three weeks after the first symptoms of nephritis were noted. As a rule, initially elevated lipid and cholesterol values reached normal levels four weeks after onset. Repeated serial de-

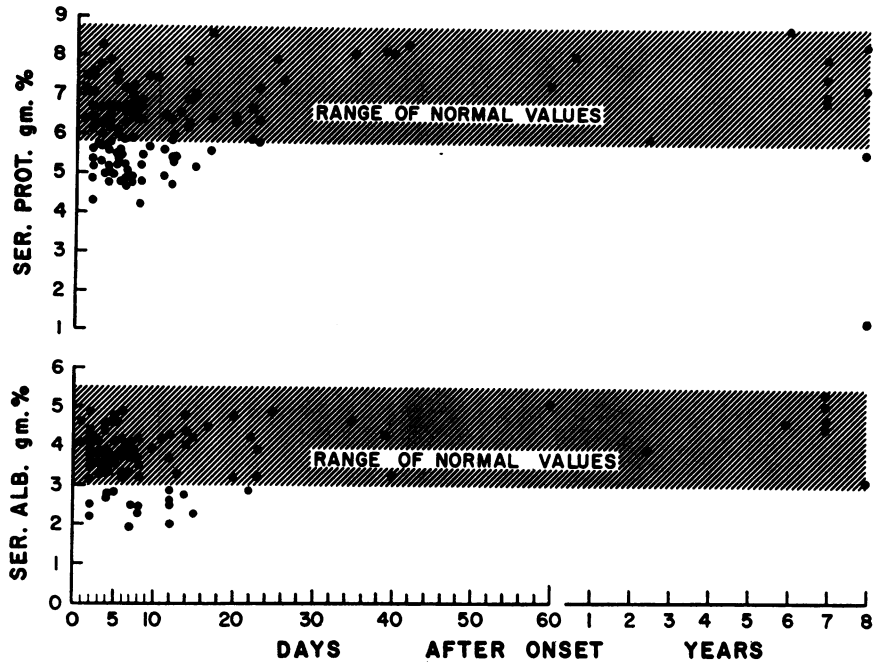

FIG. 1. SERUM PROTEIN AND SERUM ALBUMIN VALUES (GM. %) OBTAINED IN 50 AND 34 CHILDREN, RESPECTIVELY, WITH ACUTE GLOMERULAR NEPHRITIS

Shaded area represents values obtained in 58 and 53 control children, respectively.

TABLE III

Distribution of serum total lipid and cholesterol values in children with acute glomerular nephritis and controls (with and without infections)*

	Acute glomerular nephritis		Controls			
			With infections		Without infections	
	No. of cases	Per cent	No. of cases	Per cent	No. of cases	Per cent
Serum total lipids Range of values	37		7		25	
mg. %						
2,000–2,500	1	2.7	0	0	0	0
1,000–1,500	11	29.8	0	0	0	0
900–1,000	4	10.8	0	0	0	0
800– 900	4	10.8	1	14.3	1	4.0
700– 800	8	21.6	1	14.3	7	28.0
600– 700	8	21.6	3	42.8	7	28.0
500– 600	0	0	0	0	8	32.0
400– 500	0	0	1	14.3	2	8.0
300– 400	1	2.7	1	14.3	0	0
Serum cholesterol Range of values	55		29		84	
mg. %						
300– 400	8	14.5	0	0	0	0
260– 300	14	25.5	0	0	0	0
200– 260	16	29.0	3	10.2	19	22.65
150– 200	11	20.0	11	38.0	45	53.6
100– 150	6	11.0	11	38.0	19	22.6
50– 100	0	0	4	13.8	1	1.15

* First values obtained 6 to 24 days after onset of disease.

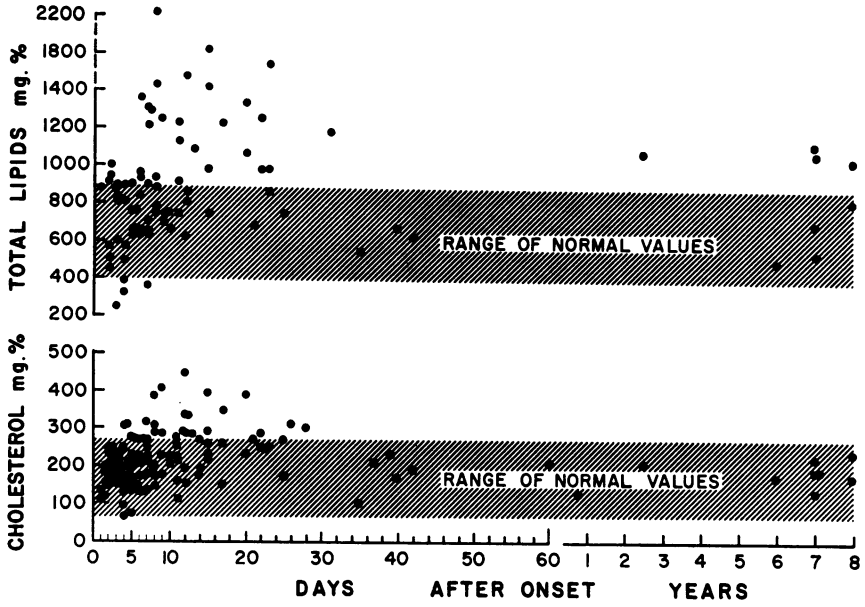

FIG. 2. TOTAL LIPID AND CHOLESTEROL VALUES IN SERUM (MG. %) OF 37 AND 55 CHILDREN, RESPECTIVELY, WITH ACUTE GLOMERULAR NEPHRITIS

Shaded area represents range of normal values obtained in 32 and 113 control children, respectively.

terminations were obtained in three patients and their values are reproducd in Table IV. It can be seen that in Patient No. 2 serum cholesterol concentration was still increased three months after onset, and that in Patient No. 1 cholesterol and total lipid values had not returned to normal values eight months after onset even though urine examination did not reveal any abnormality at this time. In Patient No. 1 total lipid values were still markedly elevated one month after onset. It is worthy of note that these increased values for serum lipids were obtained at a time when serum protein and albumin values had returned to normal three to six months previously.

Table V lists the distribution, mean and median values for serum cholesterol and total lipid con-

TABLE IV

Behavior of serum protein, serum albumin, serum cholesterol and total lipids in three children with acute glomerular nephritis followed up to eight months after onset

	Weeks after onset				Months after onset				
	1	2	3	4	2	3	5	6	8
Patient No. 1									
Serum protein (*Gm. %*)	4.6	6.7			6.2		7.0		7.6
Serum albumin (*Gm. %*)	2.4	3.6					4.5		5.0
Cholesterol (*mg. %*)	382	420			375		296		270
Total lipids (*mg. %*)	1,480				1,180		1,350		900
Patient No. 2									
Serum protein (*Gm. %*)		5.2	6.0	6.9		7.2		7.7	
Serum albumin (*Gm. %*)		2.6	3.4			3.7		5.5	
Cholesterol (*mg. %*)		270	270	290		345		230	
Total lipids (*mg. %*)		1,250	960	1,100		550		710	
Patient No. 3									
Serum protein (*Gm. %*)	4.9	5.3	6.3						8.6
Serum albumin (*Gm. %*)	1.9	2.4	3.1						4.6
Cholesterol (*mg. %*)	318	392	391						223
Total lipids (*mg. %*)	1,210	1,580	1,340	1,680					710

TABLE V

Bacteriologically and/or serologically confirmed cases of acute glomerular nephritis

	Acute glomerular nephritis		Controls	
	No. of cases	Per cent	No. of cases	Per cent
Serum total lipids Range of values	37		32	
mg. %				
300– 400	2	5.4	0	0
400– 500	0	0	3	9.4
500– 600	4	10.8	9	28.1
600– 700	3	8.1	10	31.3
700– 800	5	13.5	8	25.0
800– 900	6	16.2	1	3.1
900–1,100	8	21.7	1	3.1
1,100–1,500	6	16.2	0	0
1,500–2,000	2	5.4	0	0
2,000–2,500	1	2.7	0	0
Average (*mg. %*)	921		629	
Median (*mg. %*)	857		634	
Serum cholesterol Range of values	47		92	
mg. %				
90– 100	1	2.12	1	1.1
100– 150	7	14.9	21	22.7
150– 200	14	29.8	48	52.2
200– 250	11	23.4	20	21.8
250– 300	10	21.2	2	2.2
300– 350	2	4.25	0	0
350– 400	0	0	0	0
400– 450	2	4.25	0	0
Average (*mg. %*)	216		172	
Median (*mg. %*)	205		175	

centration obtained in 47 to 37 cases, respectively, in whom the diagnosis of acute glomerular nephritis was supported by positive throat cultures for beta hemolytic streptococci or by antistreptolysin titers greater than 333. A statistical evaluation of this material reveals that total lipid as well as cholesterol values were more frequently higher than normal in the serum of the nephritic patients ($p < 0.01$).

DISCUSSION

It should be pointed out that the 111 cases of glomerular nephritis in whom serum protein and/or albumin, cholesterol and/or total lipid values were obtained represented a group of unselected cases of acute glomerular nephritis.

Doubt could arise as to whether or not the diagnosis of acute glomerular nephritis was correct in every case studied. The usual criteria for the diagnosis were used as outlined before. None of the cases used in this study has to our knowledge relapsed or shown evidence of chronic renal disease. Bacteriological and serological tests obtained in support of the diagnosis and re-examinations performed have been previously mentioned. From the 39 patients with acute glomerular nephritis that had increased cholesterol or total lipid values during the acute phase of the disease, 26 (67 per cent) were re-examined more than two months after onset of the disease. Twelve were seen two months to one year after onset, and 14, one to nine years after onset. Negative urine examinations, normal blood pressure readings, blood urea nitrogen (BUN) values and red blood cell sedimentation rates were obtained in all. If doubts were to be maintained as to whether or not a case of nephrosis may have been included in our series, it should be pointed out that statistically significantly higher serum cholesterol and total lipid values were also obtained in the 47 cases of nephritis that were bacteriologically or serologically supported by either positive throat cultures for beta hemolytic streptococci or antistreptolysin "O" titers greater than 333.

Hypoproteinemia and hypoalbuminemia in early phases of glomerulonephritis have been described by others prior to this study (11–13). The degree of proteinuria in acute glomerular nephritis is usually not severe enough to explain satisfactorily the depletion of plasma proteins. Hydremia has been noted in the edematous stage of this disorder (12, 14). At least in part, this may play a role in the pathogenesis of hypoproteinemia and hypoalbuminemia of acute glomerular nephritis.

We believe that our studies have shown that a mild to moderate degree of hyperlipemia may be noted in 40 to 43 per cent of children suffering from acute glomerular nephritis. The finding of moderately increased serum cholesterol or total lipid values thus no longer should exclude the diagnosis of acute glomerular nephritis. Hyperlipemia is almost invariable in children with the nephrotic syndrome.[2]

[2] At a recent "Yearly Conference on the Nephrotic Syndrome" the participants were asked whether they had ever seen a child in the active phase of the disease without hyperlipemia. None of them had. The combined experience of these participants must have comprised more than 500 cases. In our own experience with 219

It has been proposed (15) that in the nephrotic syndrome hypoalbuminemia plays a causal role in the elicitation and maintenance of the nephrotic hyperlipemia. An evaluation of the data presented in this communication, obtained in children suffering from acute glomerular nephritis, reveals that of 35 total lipid values that were above normal range, 12 were obtained in children in whom serum albumin values were lower than normal, whereas 23 (65 per cent) were noted in children with normal serum albumin values. Of 16 hypercholesteremic values, nine had hypoalbuminemia whereas the remaining seven (or 44 per cent) were obtained in sera with albumin concentrations within normal range. Considering further that the nephritic hypoalbuminemia may be due to a great extent to hydremia rather than to urinary losses of albumin, we doubt that our data support the hypothesis (15) of a causal relationship between hypoalbuminemia and hyperlipemia.

Both hypoalbuminemia and hyperlipemia, whenever noted in acute glomeruler nephritis, are less severe than in the nephrotic syndrome. If, however, hypoproteinemia and hyperlipemia may occur in early stages of acute glomerular nephritis, and if for a few days proteinuria, edema and ascites may in some of these children be marked, a mild and transient nephrotic syndrome then may be noted. Six of our 111 cases presented this picture. Inasmuch as hematuria no longer serves as a valuable aid in the differential diagnosis between nephritis and nephrosis (1, 10, 16, 17), other procedures have to be resorted to. Bacteriological and serological tests have proved their value in supporting the diagnosis of glomerular nephritis from an etiological point of view. Nose and throat cultures are of obvious importance if they yield beta hemolytic streptococci (18). The type specificity of these organisms for nephritogenic strains can be determined and can be most helpful. Antistreptolysin "O" titers yield low values in the nephrotic syndrome and are usually greater than 333 in acute glomerular nephritis. In single instances one might have to wait for the course of the disease to decide the diagnostic problem. In acute glomerular nephritis a benign course would be expected, while in nephrotic children with hematuria a benign course with rapid clearing would be most unusual.

children suffering from the nephrotic syndrome and seen during the last 26 years at Babies and Children's Hospital, hypercholesteremia and/or hyperlipemia was noted in every instance.

SUMMARY

1) In 111 children suffering from acute glomerular nephritis, serum protein, albumin, cholesterol and total lipid values were obtained during early stages of the disease. These were compared with corresponding values obtained in 123 controls of similar age. Twenty-three of these had recent infections, while 98 had been free of infection and were free of any condition that conceivably may have an effect on serum protein or lipid concentration.

2) Lower values for serum protein and albumin concentration than any obtained in the controls were noted in 20 per cent of the nephritic group. In these, hypoproteinemia and albuminemia were most marked 2 to 15 days after onset and persisted for as long as 23 days.

3) Higher values for serum cholesterol and total lipid concentration than any obtained in the control group were noted in 40 per cent and 43 per cent, respectively, of the children with acute glomerular nephritis. This mild to moderately severe hyperlipemia may be observed as early as two to four days after onset and the highest values were obtained one to three weeks after first symptoms of the disease had been noted. A return to normal levels was usually observed after four weeks, though some took as long as three to eight months to reach the normal range.

4) The presence of mild to moderately severe hyperlipemia should no longer be considered to exclude acute glomerular nephritis. Bacteriological and serological confirmation of the diagnosis of glomerular nephritis by obtaining nose and throat cultures and antistreptolysin "O" titers is recommended.

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