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Variations in Serum Complement in the Nephrotic Syndrome and other Forms of Renal Disease

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Summary. Serial complement determinations have been carried out in 75 patients suffering from various forms of renal disease. Very low serum complement levels were found during the early active stage of acute nephritis, but these low values returned to normal in most cases in parallel with clinical recovery. Moderately depressed complement levels were found in subacute nephritis. These values returned to normal whether clinical recovery occurred or whether the patient progressed to chronic nephritis with or without terminal renal failure. Cases of chronic nephritis, chronic pyelonephritis or of chronic renal damage from other causes gave normal complement values.

Serum complement values were similar when cases with and without the nephrotic syndrome were matched, as far as possible, according to the underlying disease process. Cases of the nephrotic syndrome of undetermined aetiology were divisible into a group with subnormal values and a group with persistently normal values. It is suggested on the basis of the foregoing observations that these two groups may be aetiologically distinct.

The values of serial complement determinations as aids to diagnosis, the control of therapy (especially corticosteroid therapy) and prognosis in renal disease is appraised.

INTRODUCTION

Depression of serum complement in renal disease was first observed by Neisser and Doering (1901) in a single patient with uraemia. During a study of serum complement levels in scarlet fever, Gunn (1914–15) noted low levels in four cases complicated by nephritis. Marked depression of serum complement activity in acute nephritis was confirmed by Veil and Buchholz (1932); Kellett (1936); Kellett and Thomson (1939); Thomson, Arnott and Matthew (1939) and Reader (1948).

Lange and his colleagues (1951) working mainly with children were the first to draw attention to the less marked but definite depression of serum complement levels which occurs in the nephrotic syndrome. This was confirmed subsequently by Wedgwood and Janeway (1953) and by Royer, Lestradet and Seynaeve (1956) and elaborated further by Lange *et al.* (1955, 1957).

A long-term study of the aetiology and management of the nephrotic syndrome is in progress in this Department (Squire, 1953, 1955; Squire, Blainey and Hardwicke, 1957). It was decided as part of this investigation to explore the possible value of serial complement determinations as aids in the differential diagnosis, treatment and prognosis of cases of renal disease with and without the features of this syndrome. Preliminary results of this investigation of complement levels have been reported elsewhere (Ellis and Walton, 1957).

METHOD

The techniques used for the collection, handling and storage of sera and details of the method and reagents used for serial determinations of complement have been described in the preceding paper (Walton and Ellis, 1958).

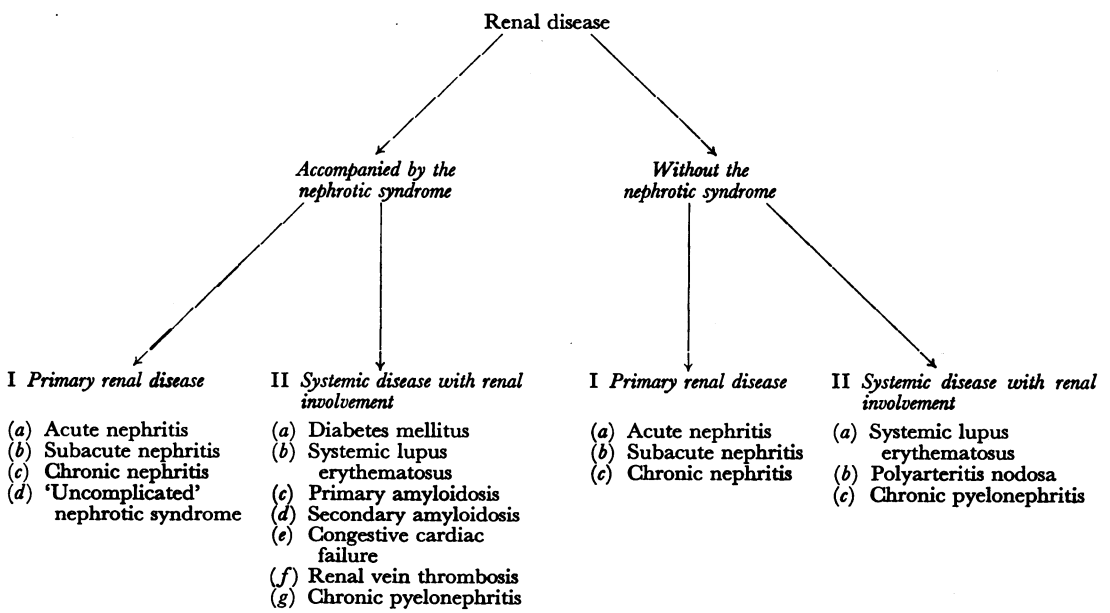
Estimation of serum and urinary proteins was carried out by the method described by Hardwicke (1954). Data made available to us concerning the investigations of nitrogen metabolism and other balance studies in the patients presently described were derived by the methods detailed by Blainey (1954). Creatinine clearances were estimated in the manner described by Owen, Iggo, Scandrett and Stewart (1954). Renal biopsy in selected cases was carried out by the method of Muehrcke, Kark and Pirani (1955).

CLASSIFICATION OF THE CASES STUDIED

For the purpose of the present study the term 'nephrotic syndrome' has been taken to denote oedema, continued proteinuria and hypoalbuminaemia (i.e. a serum albumin at some time less than 2 g. per 100 ml.). In all cases, though these features were not used as criteria for admission, the characteristic alteration in the serum globulin pattern was evident on quantitative paper electrophoresis (Squire, 1953) and hypercholesterolaemia was found in nearly every case. Similarly, renal function, as assessed by the creatinine clearance, was diminished in all but a few instances.

TABLE I

CLASSIFICATION OF CASES OF RENAL DISEASE STUDIED



Note: The primary renal disorders subacute nephritis and chronic nephritis were distinguished on the results of creatinine clearance values (subacute nephritis >30 ml. per min; chronic nephritis <30 ml. per min.), Addis counts (subacute nephritis $>20\times10^6$ red cells per 24 hours) and in some cases by renal biopsy.

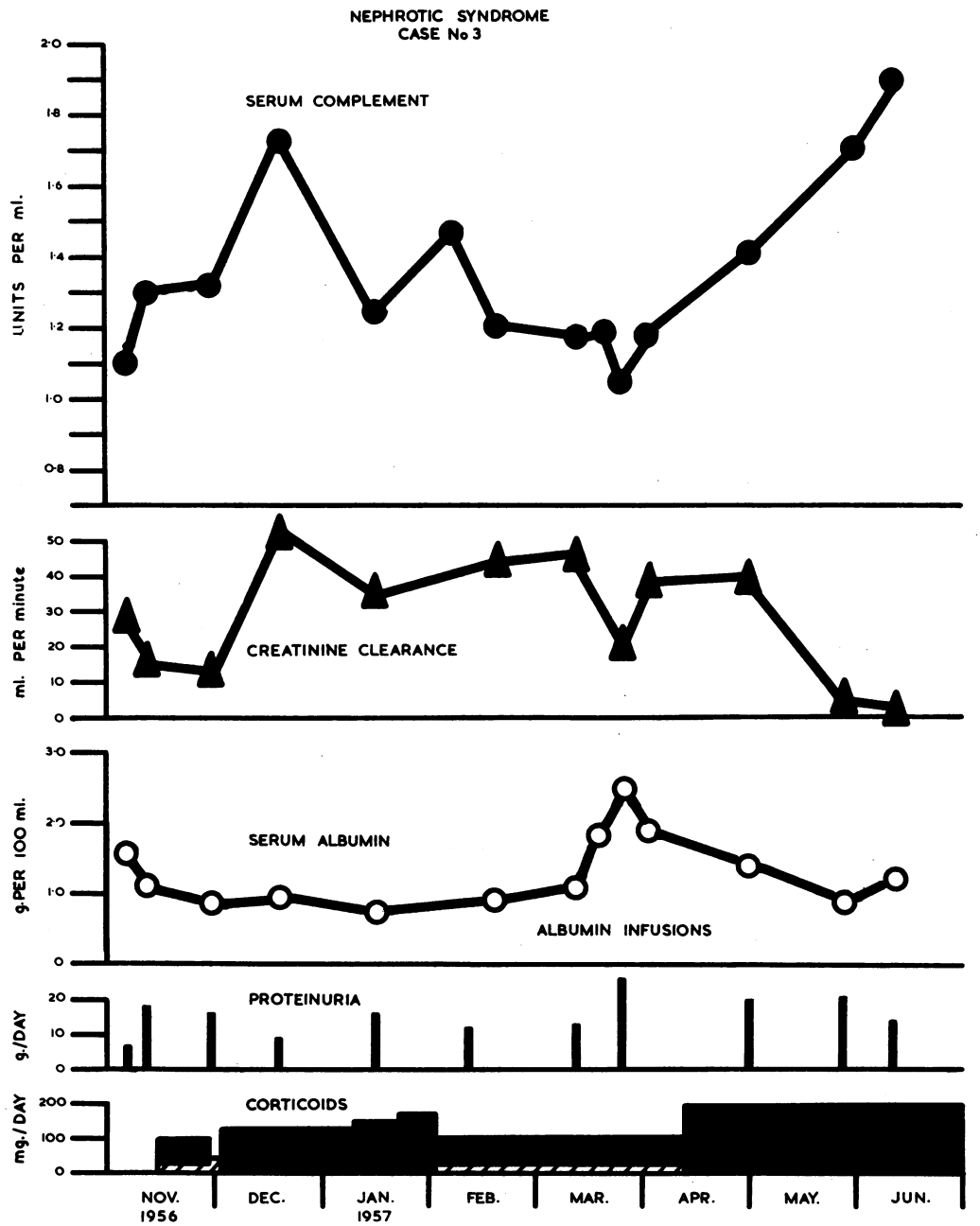


FIG. 1. Behaviour of serum complement in a fatal case of the nephrotic syndrome. Solid blocks, cortisone; cross-hatched blocks, prednisone.

This clinical syndrome can occur in primary renal disease or in systemic diseases with secondary renal involvement (cf. Squire, Blainey and Hardwicke, 1957). Our cases were initially divided into two major categories according to whether or not this syndrome, as defined above, was present. Further classification of the cases was attempted on an aetiological basis, as far as this was possible (see Table 1). One group of cases presented the clinical features of the syndrome but without sustained hypertension, electrolyte disorders or an appreciable excess of red blood corpuscles in the urine (less than 50×10^6 daily). The aetiological basis of the renal disorder in these cases remains undetermined. This group of cases comprised the 'uncomplicated nephrotic syndrome' (Squire, Blainey and Hardwicke, 1957).

326 tests were performed on the 75 cases of all forms of renal disease which were studied, the aim of serial testing being an evaluation of this method as a guide to progress. Particular attention was paid to patients treated with corticosteroids (cortisone or delta-corticoids), since it was hoped that serial determinations might differentiate the type of case likely to benefit from this form of therapy and possibly provide a guide to suitable dosage.

In collating the results of serial determinations in individual patients it was necessary to select a single value for each patient which could be regarded as characteristic of his disease process and to compare this with values obtained for the previously established control group. To obviate the bias which would have arisen simply from selection of the lowest value obtained in each patient the level of hypoalbuminaemia was taken as an objective criterion of the severity of the disease process. The complement value corresponding in time with the lowest serum albumin concentration was selected instead as the characteristic index of serum complement level for each given patient. In several patients, this complement value was not the lowest one recorded (see Table 2).

It had been established previously (Walton and Ellis, 1958), that the complement values for the control group corresponded a little more closely to a log-normal than to an arithmetic normal distribution curve. Conversion of the values obtained for the patients in this study to logarithm equivalents showed no significant alteration on analysis of the overall results from the uncorrected values similarly analysed.

RESULTS

I. CASES PRESENTING WITH THE NEPHROTIC SYNDROME (see Table 2)

(*A*) *Nephrotic Syndrome arising from Primary Renal Disorders*

In the single case in which the syndrome had arisen during the course of acute nephritis, the serum complement was low (0·11 unit per ml.). In cases where the syndrome was associated with subacute nephritis values ranged from 0·60 to 1·30 units per ml. with a mean of 0·99 unit per ml. (S.D. 0·37). In general, the complement value reflected the severity of the illness, the lowest values being found in the most acutely ill patients. The difference between the mean value for these groups and the mean for the control group was 3·3 times the standard error of the difference between the means and was therefore accepted as significant.

Serial observations on these patients showed that the low complement levels usually returned to normal in parallel with clinical improvement, when this occurred. However, in two cases showing eventual clinical deterioration with a fatal termination (Cases 3 and

TABLE 2

RESULTS OF SERUM COMPLEMENT ESTIMATIONS IN 42 CASES OF THE NEPHROTIC SYNDROME

Variety of the nephrotic syndrome	*Case No.*	*Sex*	*Age onset (years)*	*Duration (months) before observed*	*Period (months) of observation*	*Outcome*	*Number observations*	*Serum complement (units per ml.)*			*Remarks*
								Lowest value	*Highest value*	*Selected value*	
I. PRIMARY RENAL DISORDERS:											
(*a*) Acute nephritis ..	1	F	14	4	3	Death	8	0·11	0·46	0·11	No autopsy obtained.
(*b*) Subacute nephritis	2	M	58	23	4	Survival	5	0·85	1·29	0·85	Renal biopsy: membranous glomerulonephritis.
	3	M	35	1	8	Death	15	1·04	1·90	1·10	Renal biopsy: membranous glomerulonephritis. See Fig. 1.
	4	F	12	18	3	Death	4	0·60	1·30	0·60	Case 7. Squire *et al.*, 1957.
	5	M	41	13	12	Survival	7	1·26	1·74	1·26	Case 8. Squire *et al.*, 1957. Recovering at first examination.*
	6	F	25	16	14	Survival	9	0·98	1·74	1·30	Case 19. Squire *et al.*, 1957. Renal biopsy: normal.
	7	M	39	2	15	Survival	10	1·00	1·34	1·07	Case 23. Squire *et al.*, 1957. Renal biopsy: membranous glomerulonephritis.
	8	M	49	27	10	Survival	4	1·08	1·30	1·30	Case 6. Squire *et al.*, 1957.
	9	M	28	28	18	Survival	11	0·75	0·93	0·80	Case 40. Squire *et al.*, 1957. Renal biopsy: membranous glomerulonephritis. Also had renal vein thrombosis.
	10	F	32	2	10	Survival	5	0·96	1·47	1·17	—
(*c*) Chronic nephritis	11	F	29	12	10	Survival	6	1·22	1·46	1·22	Renal biopsy: chronic nephritis.
	12	M	52	14	4	Death	6	1·45	1·60	1·60	Renal biopsy: chronic nephritis.
	13	M	43	3	0	Death	1	—	—	2·0	Autopsy: chronic nephritis.
(*d*) 'Uncomplicated' nephrotic syndrome	14	F	5	8	5	Survival	4	0·97	1·82	0·97	Observed during relapse and recovery.
	15	M	6	13	12	Survival	17	0·65	1·45	0·80	Case 13. Squire *et al.*, 1957. See Fig. 2.
	16	M	17	68	11	Survival	10	0·98	1·29	1·16	Case 11. Squire *et al.*, 1957. Observed during relapse.
	17	M	48	17	9	Survival	2	1·48	1·76	1·49	—
	18	M	15	0	4	Survival	10	1·04	1·78	1·20	—
	19	M	39	76	18	Survival	9	0·91	1·78	0·91	Case 14. Squire *et al.*, 1957. Observed in relapse. Renal biopsy: glomeruli normal. Tubular degenerative changes.

	20	M	44	3	16	Survival	11	0·98	1·69	0·98	Renal biopsy: membranous glomerulo-nephritis.
	21	F	54	1	17	Survival	17	0·95	2·10	0·95	See Fig. 3.
	22	M	41	16	13	Survival	8	1·16	1·59	1·16	Case 10. Squire *et al.*, 1957. Recovering at first examination.*
	23	F	46	11	14	Survival	6	1·37	1·77	1·37	Case 17. Squire *et al.*, 1957. Recovering at first examination.*
	24	M	52	14	8	Survival	3	1·38	1·57	1·38	Case 12. Squire *et al.*, 1957. Recovering at first examination.*
	25	M	27	5	0	Survival	1	—	—	1·10	—
	26	M	70	60	0	Survival	1	—	—	1·37	Recovering at first examination.*
	27	M	2	7	0	Survival	1	—	—	0·95	—
	28	M	56	1	8	Survival	8	1·63	2·05	1·63	—
	29	M	69	18	2	Death	2	1·24	1·41	1·24	Renal biopsy: only glomerular ischaemic changes. No autopsy.
	30	M	64	4	0	Survival	1	—	—	1·86	—
II. Nephrotic Syndrome Complicating:											
(*a*) Diabetes mellitus	31	M	33	3	0	Death	1	—	—	1·48	Autopsy: typical Kimmelstiel-Wilson lesions.
	32	F	33	—	0	Survival	1	—	—	2·19	Known diabetic for fourteen years.
	33	M	44	15	0	Death	1	—	—	1·60	Autopsy: typical Kimmelstiel-Wilson lesions.
(*b*) Systemic lupus erythematosus	34	F	37	3	0	Survival	1	—	—	0·18	—
	35	M	28	2	11	Survival	7	0·11	0·95	0·11	Case 28. Squire *et al.*, 1957. See Fig. 6.
(*c*) Primary amyloidosis	36	M	68	14	4	Death	4	1·84	2·05	1·84	Autopsy: amyloidosis. Case 31. Squire *et al.*, 1957.
(*d*) Secondary amyloidosis	37	M	22	1	0	Survival	1	—	—	2·27	Case 29. Squire *et al.*, 1957. Still's disease: confirmed amyloid histologically.
	38	M	38	1	13	Survival	4	1·35	1·40	1·35	Pulmonary tuberculosis. Renal biopsy: amyloid.
(*e*) Congestive cardiac failure	39	M	61	6	9	Survival	9	1·37	1·57	1·37	Also possible toxic effects of mercurials.
	40	M	48	7	10	Survival	2	1·48	1·77	1·48	—
(*f*) Renal vein thrombosis	41	F	55	11	12	Death	7	1·61	1·82	1·61	Case 18. Squire *et al.*, 1957. See Fig. 4. Confirmed at autopsy.
(*g*) Chronic pyelonephritis	42	F	45	6	10	Survival	6	1·04	1·40	1·04	Case 44. Squire *et al.*, 1957.

* Excluded from analysis.

4, Table 2) complement values also rose to within the normal range during the final phase of renal failure. This pattern is illustrated in Fig. 1 (Case 3, Table 2). In this case the complement values at the outset were at the lower limit of the normal range. After the initiation of therapy with cortisone, complement values rose rapidly in parallel with clinical improvement and an improved creatinine clearance. This remission was short-lived and complement values declined once more in company with a slowly declining creatinine clearance and gradual clinical deterioration. It was interesting to observe that a short period of therapy with albumin infusions produced a rise in serum albumin but no

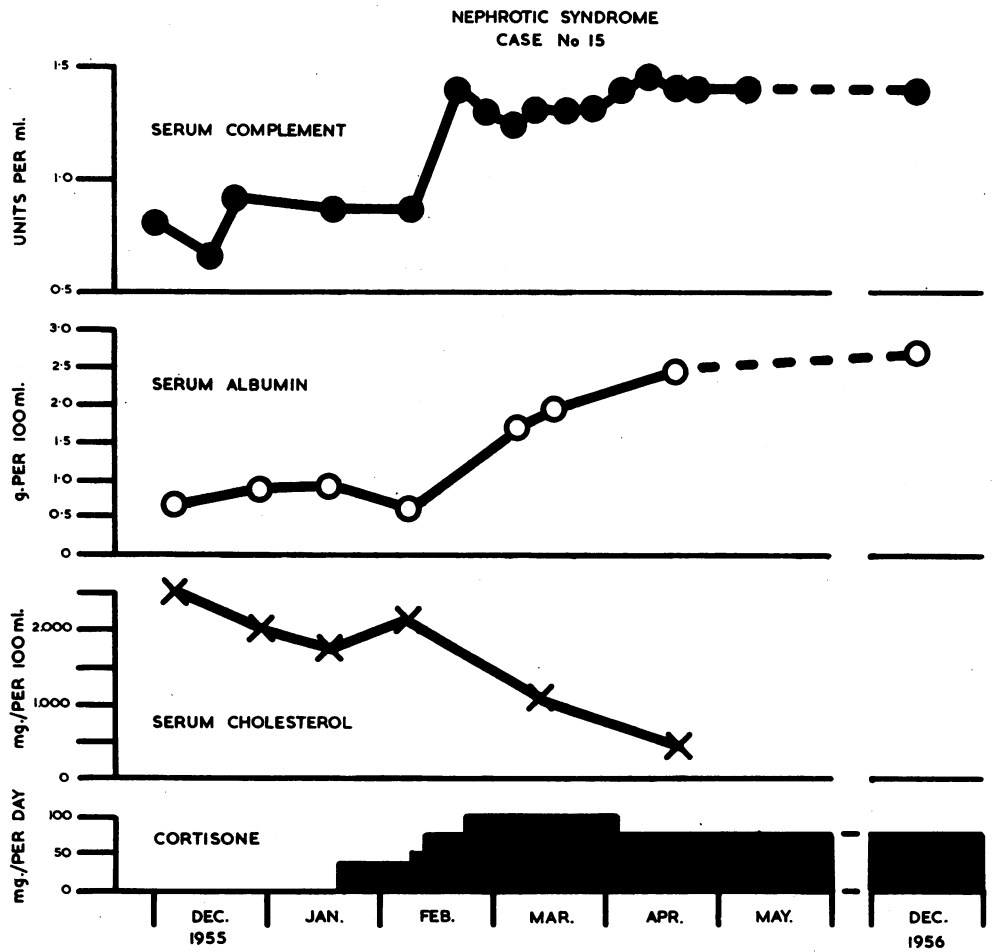


FIG. 2. Return of serum complement to normal in a child suffering from the nephrotic syndrome. Note the coincident fall in serum cholesterol and rise in serum albumin.

significant change in serum complement. However, during the three months before death a definite progressive rise in complement values occurred, this time in association with further deterioration in renal function. The clinical and pathological evidence in this case suggested that the renal disease had advanced into the chronic phase in which complement values are known to be normal (see below).

Where the syndrome had arisen in association with chronic nephritis (creatinine clearance consistently below 30 ml. per minute), the serum complement levels were well within the normal range in the three cases examined.

One case (Case 9, Table 2) accepted initially on clinical grounds as renal vein thrombosis showed unremitting complement values at about the lower limit of normal (0·75 to 0·93 unit per ml.). Renal biopsy showed glomerular changes suggestive of membranous glomerulonephritis (Kark, Muehrcke, Pirani and Pollak, 1955). Whether the renal changes developing either independently or secondarily to the renal vein thrombosis had brought this patient's values into line with those of the group classifiable as 'subacute

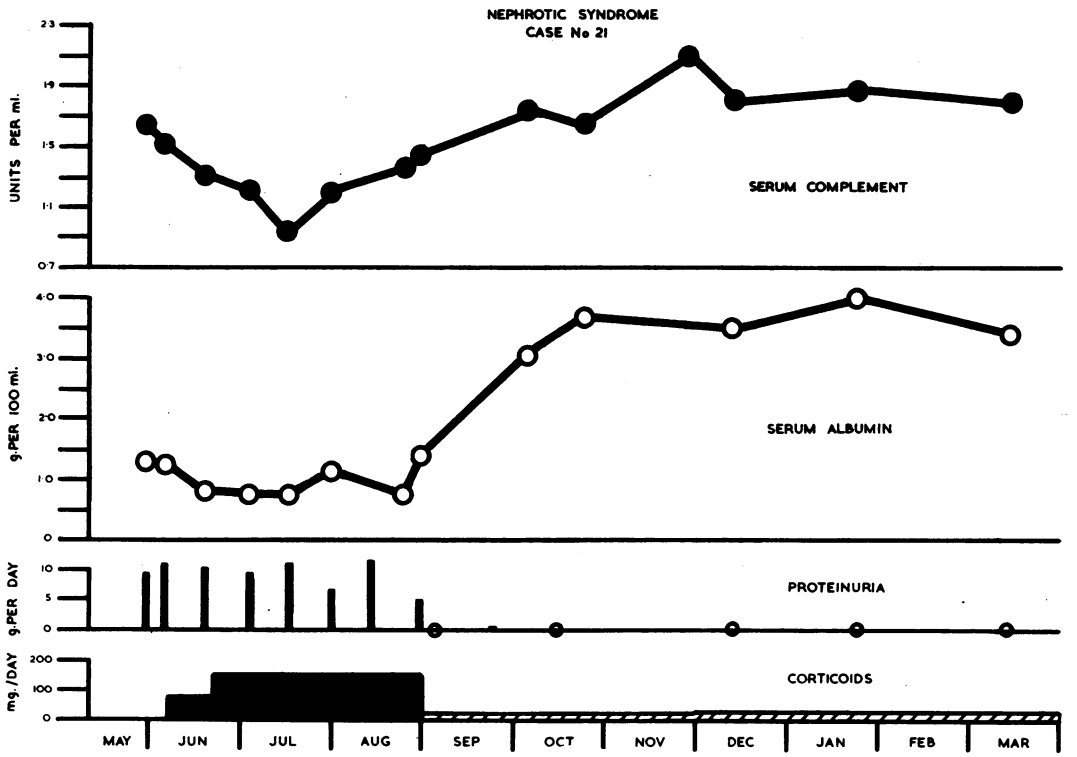


FIG. 3. Behaviour of serum complement in a case of the nephrotic syndrome showing recovery. Note the fall in serum complement during the initial period of observation and subsequent rise in parallel with recovery.

Solid blocks, cortisone; cross-hatched blocks, prednisone.

nephritis', or whether the slightly lowered level was merely an innate characteristic of this patient, remained undecided.

'Uncomplicated' Nephrotic Syndrome. In this group the range of values obtained was from 0·80 to 1·86 units per ml. of serum, with a mean of 1·17 units per ml. (S.D. 0·31). The difference between the mean of this group and the control group mean was 2·9 times the standard error of the difference between the means and this was accepted as a significant difference. In this group serial determinations showed two different patterns of variation:

(i) An initially low serum complement which returned to normal with clinical improvement (8 cases). This pattern is illustrated in Fig. 2 (Case 15), from which it can be seen

that when the patient came under observation the serum complement was low and remained so with the initial dosage of cortisone. When the dosage of cortisone was increased the serum complement rose rapidly to normal in parallel with a rise in serum albumin and clinical improvement. The state has been maintained up to the present time.

A further case (Case 21, Table 2) showed a variant on this pattern in that serum complement was initially normal, fell during the early stages of the illness and returned to

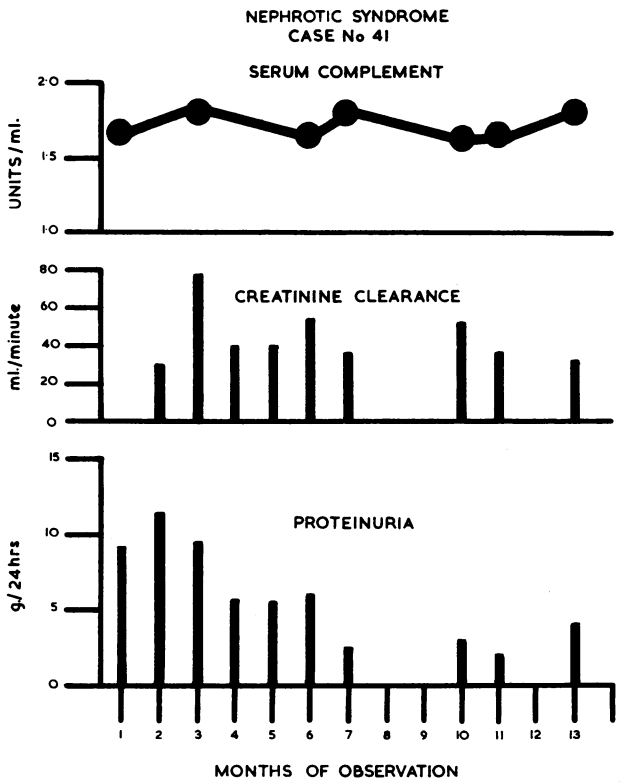


FIG. 4 Persistently normal serum complement in a fatal case of the nephrotic syndrome. This patient was thought to be suffering from 'uncomplicated' nephrotic syndrome throughout the many months of her illness. At autopsy a renal vein thrombosis was found to be the underlying cause of the syndrome.

normal with clinical improvement. This patient was an adult female who was first seen within a few weeks of onset of her illness, at which time the serum complement was normal. During the first two and a half months of treatment with cortisone her clinical condition deteriorated and this was associated with a fall in serum complement. There followed a period of clinical improvement paralleled by a return of serum complement to normal, where it has remained subsequently. This patient remains well on continuous cortisone therapy with a normal serum complement fourteen months after the onset of her illness. Her progress is illustrated in Fig. 3.

(ii) In 5 cases the serum complement levels remained within normal limits throughout the illness with insignificant fluctuations bearing no relation to the clinical picture. It is

possible that these cases were aetiologically unrelated to those showing the preceding pattern of complement variation. To illustrate this point one additional case (Case 41, Table 2), a 55-year-old female, was initially classified as 'uncomplicated' nephrotic syndrome throughout many months of illness. The serum complement was persistently within the normal range when estimated at monthly intervals for just over a year (see Fig. 4). During this period only a moderate clinical improvement was observed in response to cortisone therapy and this was not reflected in any change in serum complement levels. When this case came to autopsy it became clear that a renal vein thrombosis was the underlying cause of her condition.

In four further cases complement values were within normal limits. These cases were difficult to evaluate since clinical and biochemical evidence of recovery was already evident in each case when the patient was tested for the first time.

(B) Nephrotic Syndrome complicating Generalised Disease

The miscellaneous general diseases found to underlie the nephrotic syndrome in this group are listed in Table 2. It will be seen that excluding the 2 cases of systemic lupus erythematosus—a condition in which low complement levels have been recorded whether or not the disease is complicated by renal involvement (Vaughan, Bayles and Favour, 1951; Wedgewood and Janeway, 1953; Elliott and Mathieson, 1953)—the remaining 10 cases showed complement values ranging from 1·04 to 2·27 units per ml. with a mean of 1·62 units per ml. (S.D. 0·40). The difference between the mean and the control mean was 1·46 times the standard error of the difference between the means, which was not significant. Serial estimations showed that serum complement values remained within the normal range throughout the periods of observation.

II. CASES WITHOUT THE NEPHROTIC SYNDROME

Estimation of complement levels in cases of renal disease which did not present the features of the nephrotic syndrome gave results similar to those with the nephrotic syndrome (i.e. very low values in acute nephritis, moderately low values in subacute nephritis, and normal values in chronic nephritis and in chronic renal disease from other causes (see Table 3). It was therefore concluded that the development of the nephrotic syndrome in

TABLE 3

COMPARISON OF SERUM COMPLEMENT LEVELS IN RENAL DISEASE

Type of renal disease	*With nephrotic syndrome*		*Without nephrotic syndrome*	
	No. of cases	*Mean (units/ml.)*	*No. of cases*	*Mean (units/ml.)*
Acute nephritis	1	0·11	13	0·38
Subacute nephritis	9	1·05	2	1·07
Chronic nephritis	3	1·61	9	1·38
'Uncomplicated' nephrotic syndrome	17	1·17	—	—
Systemic lupus erythematosus and polyarteritis nodosa	2	0·15	2	0·38
Chronic pyelonephritis	1	1·04	7	1·32
Diabetes, amyloidosis, renal vein thrombosis and congestive cardiac failure	9	1·68	—	—

cases of renal disease is not, in itself, a factor determining the level of serum complement. Accordingly, in summarising the total experience accruing from this study cases have been reclassified primarily in relation to the stage of nephritis (acute, subacute or chronic) present, without reference to the additional presence or absence of the nephrotic syndrome. The remaining cases have then been allotted to two further sub-groups: one in which the precise nature of the renal disease underlying the syndrome was indeterminable ('uncomplicated nephrotic syndrome') and the other in which the nephrotic syndrome arose as a complication of known generalized disease. The results thus rearranged are summarized in Fig. 5.

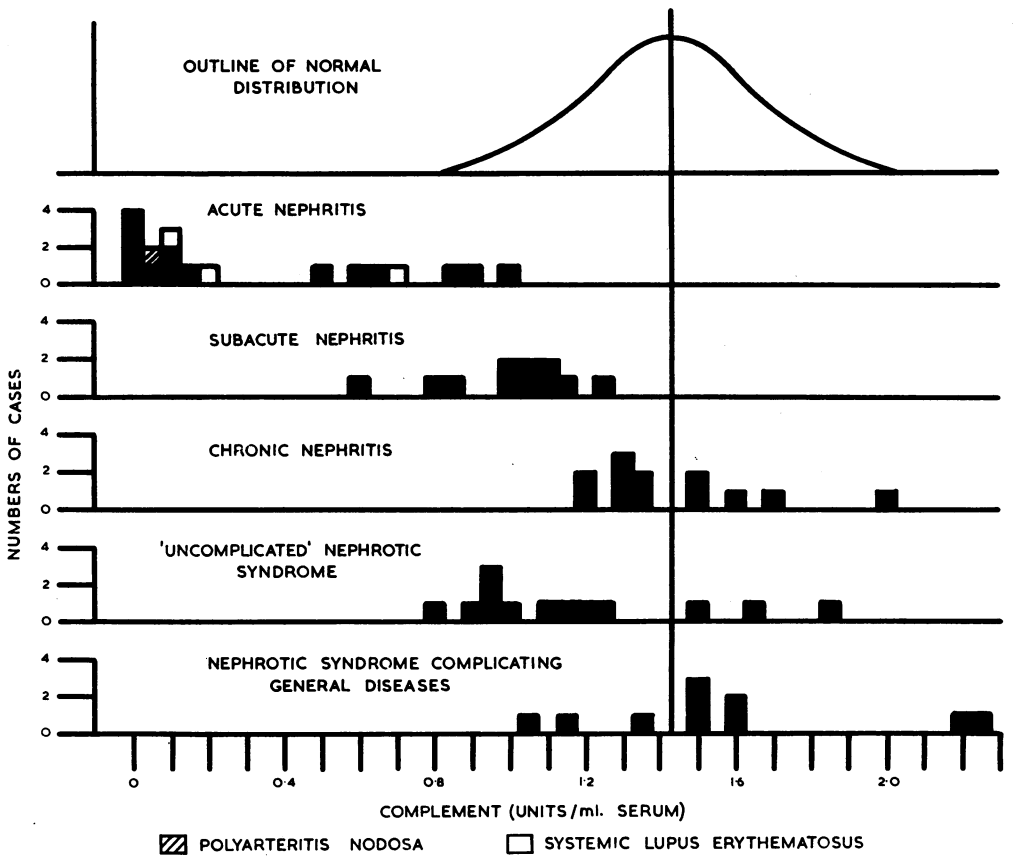


FIG. 5. Summary of serum complement results in all cases studied.

RELATION OF VARIATIONS IN COMPLEMENT LEVELS TO NATURE AND SEVERITY OF RENAL DISEASE AND PLASMA PROTEIN CHANGES

The most marked changes in serum complement levels were observed during the initial and most active phase of acute nephritis (see Table 4). At this stage, serum complement was invariably very low or apparently completely absent. In 3 out of the 4 cases in which no complement activity was demonstrable, the sera were found to be anticomplementary (i.e. after inactivation by heating at 56° C. for 25 minutes these sera inhibited the complementary activity of normal serum). The serum proteins were estimated differentially

by paper electrophoresis in 11 of the 14 cases of acute nephritis studied. The main feature of note was an almost invariable elevation of the gamma globulin fraction (mean 1·79 g. per 100 ml.; range 0·82 to 3·10 g. per 100 ml. as compared with normal range of 0·80 to 1·40 g. per 100 ml.

TABLE 4

RESULTS OF SERUM COMPLEMENT ESTIMATIONS IN 14 CASES OF ACUTE NEPHRITIS

Case No.	*Age at onset (years)*	*Sex*	*Complement units/ml.*	*Estimated corresponding day of illness*	*Outcome*	*Remarks*
1	14	F	0·11 to 0·27	4th-7th month	Death	
43	45	M	0	30	Recovered	Clinically a mild case of acute nephritis, but complement took several months to return to normal. (Serum anticomplementary.)
			0·13	78		
			0·64	107		
			1·28	141		
44	14	F	1·02	18	Recovered	Acute nephritis recovering at time of examination.
45	32	F	0	9	Recovered	Serum anticomplementary.
			0	16		
46	2	M	0·06	7	Recovered	
			0·09	14		
47	11	F	0·25	22	Death	Death in uraemia, 41st day. Acute nephritis confirmed at autopsy.
			0·14	36		
48	5	M	0·50	7	Recovered	
49	66	F	0·35	21	Death	Death in uraemia, 47th day. Acute nephritis confirmed at autopsy.
			0·12	30		
50	12	M	0·90	34	Recovered	Acute nephritis. Recovering at time of first examination.
51	13	M	0	7	Recovered	Serum not anticomplementary.
			0·49	17		
			1·18	65		
52	6	F	0·67	10	Recovered	
			0·69	17		
			0·71	24		
			0·97	45		
53	12	M	0·86	23	Recovered	Acute nephritis recovering at time of first examination.
54	8	F	0	5	Recovered	Serum anticomplementary in early stage of illness.
			0	15		
			0	22		
			1·42	65		
55	3	F	0·60	8	Recovered	

Although in most of the cases which showed clinical recovery the complement values rose rapidly to normal as the proteinuria diminished and ceased, one case (Case 43, Table 4) was exceptional in that it was five months from the onset of the illness before the serum complement was restored to the normal level, in spite of an apparent full clinical recovery two months earlier.

While hypergammaglobulinaemia was a feature of the acute phase when complement levels were very low, no correlation between gamma globulin and complement levels was observed during the subsequent course of these cases since, in most instances the gamma globulin remained elevated long after the complement values returned to normal, while in Case 43 (referred to above), in whom the restoration of complement to normal was delayed, the elevation of the gamma globulin fraction during this lag phase was not pronounced. Thus, although normal serum gamma-globulin has been found to inhibit complement activity (Davies, 1944; Olhagen, 1945), it is difficult for us to accept

the preponderance of this globulin fraction as the only reason for the low levels encountered in acute nephritis.

Attempts were also made to relate alterations in serum complement to alterations in the total serum proteins or in the individual serum proteins (albumin, alpha, beta and gamma globulins) during the course of subacute nephritis with or without the nephrotic syndrome. No such relation was discernible.

III. MISCELLANEOUS DISORDERS WITH SECONDARY RENAL INVOLVEMENT

Amongst the group of miscellaneous disorders with secondary renal involvement, low complement values were encountered only in the three cases of systemic lupus erythe-

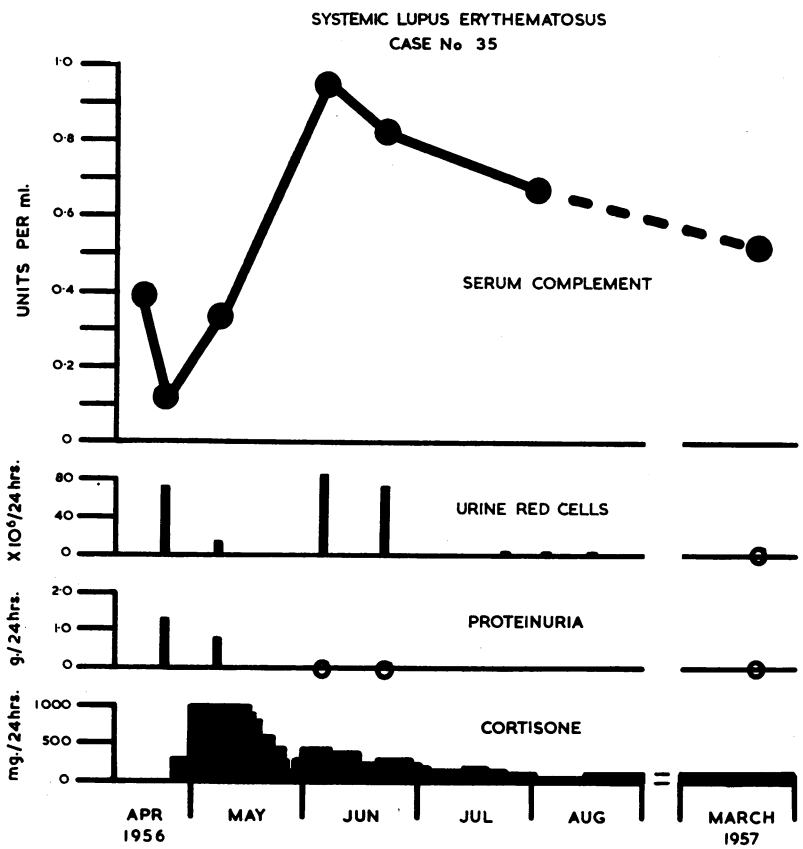


FIG. 6. Behaviour of serum complement in a 28-year-old male suffering from systemic lupus erythematosus treated with cortisone.

matosus (S.L.E.) examined and in the single case of polyarteritis nodosa encountered. These cases deserve further consideration:

Systemic Lupus Erythematosus

All three cases were shown to have L.E. cells in the peripheral blood and two of the three exhibited the nephrotic syndrome at some stage of their disease. All the cases showed

subnormal complement values and the persistence of this level, in spite of a good clinical response to therapy in one case (Case 35) the progress of which is illustrated in Fig. 6, provided an interesting illustration of the value of serial complement determinations in this condition. The patient showed a remarkable clinical recovery in response to intensive cortisone therapy and this was associated with a rise in serum complement from very low levels to just subnormal ones. That this persistence of a subnormal complement level indicated continued activity of the disease process in spite of an apparently complete clinical remission was strongly suggested by the finding of active lesions in occasional glomeruli in renal biopsy material at the end of the period indicated in Fig. 6.

Polyarteritis Nodosa

The single case studied merits special mention because of certain unusual features.

A 22-year-old female was admitted with headache, peripheral oedema, proteinuria and haematuria. The initial diagnosis was acute nephritis. The serum complement was low (0·05 unit per ml.) which was in conformity with this diagnosis. On storing the serum at 4° C., a flocculent white precipitate separated but redissolved on warming the serum to room temperature. This cryoglobulin was separated and found to be indistinguishable from gamma-globulin in having similar electrophoretic mobility and in reacting normally with a rabbit anti-human gamma-globulin antiserum in spite of its atypical solubility characteristics. The isolated protein was actively anticomplementary, there being a rise in complement activity in the patient's serum on removing the protein and a depression of the complement level of normal serum on adding the isolated and washed cryoglobulin.

At autopsy, lesions typical of polyarteritis nodosa were demonstrable in the kidneys and other organs in this patient.

DISCUSSION

DIAGNOSTIC AND PROGNOSTIC VALUE OF SERIAL COMPLEMENT DETERMINATIONS IN RENAL DISEASE

The serum complement levels found to be characteristic of the various stages of glomerulonephritis in the present investigation are in agreement with those previously described by other investigators.

From the diagnostic point of view, it is necessary to emphasize the lack of specificity of the results of complement determinations in renal disease. For example, although very low levels of serum complement were found to be an invariable accompaniment of the initial and active phase of acute nephritis, similar levels were also encountered in systemic lupus erythematosus, and in one case of polyarteritis nodosa initially presenting with similar clinical patterns of signs and symptoms.

Our results suggest that the development of the nephrotic syndrome during the course of renal disease does not, in itself, influence the level of serum complement. This conclusion is based on the finding that cases matched as closely as possible in relation to the nature of the underlying disease process presented similar complement values regardless of whether the nephrotic syndrome was present or absent. This conclusion is at variance with that of Lange *et al.*, who found low levels almost invariably in those of their cases which would correspond with the present 'uncomplicated' group. It should be noted that most of the cases studied by Lange *et al.* were children in whom it is possible that the

syndrome arises from a more homogeneous group of causes. Our nephrotic patients were mostly adults, and where the disease process underlying the development of the syndrome was established it was evident that many diverse pathological processes were basically responsible. In the light of this observation, even where the underlying mechanism of production of the syndrome remained undiscovered (as in our 'uncomplicated' group), it was interesting to observe that these cases were divisible into two sub-groups, one with subnormal complement values and the other with persistently normal values. The numbers so far studied are insufficient to allow the assertion that complement tests alone are sufficient to distinguish these as aetiologically different sub-groups, but at least it can be affirmed that when, in such cases, serial complement values remain persistently within the normal range during a preliminary observation period it may be suspected that either the renal disease is nephritis which has progressed to the chronic phase or is some other aetiological process such as diabetic nephropathy, renal amyloidosis or renal vein thrombosis necessitating further investigation. To this extent, complement determinations may assist in the selection of cases for renal biopsy or other investigations of renal structure and function.

It will be evident from the results quoted that complement determinations are of no value in distinguishing between chronic nephritis and chronic pyelonephritis or other chronic renal infections.

With regard to prognosis, serial complement determinations may be of assistance in gauging progress when the results are taken in conjunction with those of clearance studies. In our experience, for example, a rise in serum complement associated with an improvement in creatinine clearance was of favourable import. Contrariwise, a fall in creatinine clearance associated with a rising complement titre heralded the progression from subacute to chronic nephritis and the onset of renal failure.

COMPLEMENT DETERMINATIONS AND THE CONTROL OF CORTICOSTEROID THERAPY

The observation by Lange *et al.* (1955) that a rise in serum complement may occasionally precede clinical evidence of improvement in response to corticosteroid therapy has been confirmed. We have also observed that a persistently low level in a case treated with cortisone may be an indication that dosage is inadequate (as in Case 15 already cited). Similarly, natural relapses in cases on maintenance therapy with cortisone may be associated with a further lowering of serum complement which again may serve as an indication that an increase in cortisone dosage is desirable.

MECHANISM OF COMPLEMENT VARIATION IN RENAL DISEASE

Theoretically, lowered serum complement levels in human sera might come about in four different ways: (i) excessive loss (as for example by urinary excretion); (ii) increased utilisation (in immune reactions in the circulation or on endothelial surfaces); (iii) interaction with circulating anticomplementary substances; (iv) decreased production.

In renal disease with massive proteinuria it has naturally been suggested that loss of the protein components of complement in the urine might account for diminished serum levels. In opposition to this it has been pointed out by Lange and Wenk (1954a), and confirmed during the present study, that cases of diabetic nephropathy, renal amyloidosis and renal vein thrombosis may have urinary losses of protein as great as or greater than

cases of glomerulonephritis and yet the serum complement levels are normal in the former group of conditions. Moreover, it was shown by Lange and Wenk (1954a) that although individual complement components can be detected in the urine in proteinuria arising from many different causes, the amounts excreted were comparable whether the serum complement level was normal or not. These authors also expressed the opinion that the total urinary losses of complement were inadequate, in any case, to account for the low serum levels in some of their cases.

On the other hand, it is known that during their formation immune precipitates absorb the C'_2 and C'_4 components of complement (Pillemer, Seifter and Ecker, 1942). Lange and Wenk (1954a) have shown that these are the very components lowered in human cases of nephritis, while Lange and Wenk (1954b) have extended previous observations on the production of experimental nephritis in animals by the use of nephrotoxic antisera (Masugi, 1934; Smadel, 1936; Arnott, Kellar and Matthew, 1936; Kay, 1942; Pressman, 1949) by perfusing isolated rat kidney with nephrotoxic sera and demonstrating that glomerular damage is associated with a fall in the complement value in the perfused serum.

It would be in accord with the observed variations in serum complement levels at the different stages of human glomerulonephritis to suggest that if this disease were in fact due to structural damage arising from the union of organ-specific antibody with elements of the nephron, and if complement were absorbed during this process, then it would be expected that the lowest level of circulating complement would occur during the initial and most acute phase of this process; that less depression of complement would occur during subacute nephritis when cellular disorganization is less diffuse and intense; that least depression of complement would occur in the chronic phase when active inflammatory changes have died down and renal function is becoming progressively impaired simply by organization and fibrosis; and finally, that in these circumstances complement levels would be unrelated to the degree of proteinuria.

With regard to the lowering of serum complement by its interaction with anticomplementary substances, it was possible to demonstrate that three cases of acute nephritis in the present series had anticomplementary sera on first examination, and an anticomplementary cryoglobulin resembling gamma-globulin in many of its properties was found in one case of polyarteritis nodosa. The reasons for our non-acceptance of the hypergammaglobulinaemia characteristic of acute nephritis as the sole and continuing cause of variation in serum complement in this disease have already been discussed. This does not exclude the possibility that hypergammaglobulinaemia plays some part in determining the very low values found at the initial stages of acute nephritis.

Since nothing definite is known about the site or rate of formation of human complement in health, let alone in disease, the hypothesis that impaired production might be responsible for low serum values must remain unexplored.

In conclusion, it should be stressed that serial complement determinations if used in the management of patients suffering from renal disorders must be supplemented by accurate clinical appraisal of each individual case and must be interpreted in relation to the data available from other methods of assessing renal function.

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