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RENAL DISEASE IN SYSTEMIC LUPUS ERYTHEMATOSUS*

NAOMI F. ROTHFIELD, M.D.,† ROBERT T. MCCLUSKEY, M.D.,‡ AND DAVID S. BALDWIN, M.D.§

NEW YORK CITY

THE ability of adrenal corticosteroid therapy to prolong life in patients with systemic lupus erythematosus has been recognized by most observers.[1-3] It is generally stated, however, that the renal lesion usually progresses despite suppression of activity of the disease in other systems.[1-3] Recently, Pollak et al.[4] have suggested that "lupus glomerulonephritis" can be treated successfully by prolonged administration of corticosteroids if they are given in excess of the dosage required to control other manifestations of the disease.

We have observed a relatively low incidence of progressive renal disease in patients with systemic lupus erythematosus although steroids have been administered at the minimal dosage required to control other evidences of clinical activity. The present paper reports our observations on the course of the renal lesion on the basis of clinical observations together with pathological material obtained by renal biopsy or at autopsy.

The results show that renal disease occurs in approximately half the patients with systemic lupus erythematosus, nearly always appearing at the onset of the disease. Anatomic evidence of active damage in the kidney correlates closely with clinical evidence of activity in other systems. Administration of steroids in doses sufficient to control other systemic manifestations also appears to induce remission of the renal lesion. In rare cases severe renal disease, with rapid progression to death in renal insufficiency, is observed; our data do not permit us to conclude whether the course in such patients can be altered by prolonged administration of massive doses of steroids.

MATERIALS AND METHODS

Clinical observations were made in 52 patients with systemic lupus erythematosus. The diagnosis was based on typical multiple-system disease in addition to positive L.E.-cell preparations. All patients who were observed by us between the years 1950 and 1961 were included in the present study, except for the surviving patients who had been observed for less than one year. All patients who died on the New York University Divisions of Bellevue Hospital after 1950 were included, as were all who died at New York University Hospital after 1960. Patients were observed in Bellevue Hospital, in New York University Hospital and in the Third Division Rheumatic Disease Clinics of the Bellevue Hospital. After 1959 percutaneous renal biopsy was performed whenever possible on every patient with systemic lupus erythematosus who came under observation whether or not clinically apparent renal disease was present; between 1955 and 1959 renal biopsy was performed in an occasional patient.

Forty-seven females and 5 males, whose ages at the initial onset of symptoms ranged from eight to eighty years, were included in this study. Thirty-eight were white, 13 Negro, and 1 Chinese.

All patients were treated with corticosteroids at some time. The maximal initial daily dose was 40 to 60 mg. of prednisone or its equivalent. Most patients became asymptomatic after two to eight weeks of therapy at this dosage level. At that time the dose was gradually reduced until symptoms reappeared, and then a minimal daily dose was administered at the level required to keep the patient free of clinical manifestations of active disease. The average daily "maintenance" dose was 10 mg. of prednisone, with a range of 2.5 to 20.0 mg. From time to time an attempt was made to reduce further the daily dose. A few patients continued in clinical remission without corticosteroid therapy. Most patients were also maintained on chloroquine.

Fever or manifestations in at least one organ other than the kidney were considered evidence of active disease.[5] Proteinuria alone was not considered an indication for a raise in the steroid dose. Clinical activity, such as fever, arthritis, rash, mucosal ulcers or hair loss, was treated by an increase in the daily steroid dose by increments of 2.5 to 15.0 mg. until evidence of activity had disappeared. The dose was then slowly

*From the departments of Medicine and Pathology, the Rheumatic Diseases Study Group and the Hypertension and Renal Diseases Study Group, New York University School of Medicine, and the Third and Fourth (New York University) Medical Divisions, Bellevue Hospital.

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†Instructor, Department of Medicine, New York University School of Medicine.

‡Professor of pathology, New York University School of Medicine.

§Assistant professor, Department of Medicine, New York University School of Medicine.

reduced to the previous level, or lower if possible. The patients were instructed to get in touch with the physician immediately upon the appearance of fever or other symptoms.

Renal tissue from 32 patients was examined. Twenty-four renal biopsies were performed in 20 patients, according to the technic of Kark and Muehrcke.[6] Autopsy material was examined in 3 patients in whom biopsies had been performed and in an additional 12 patients.

Biopsy material was usually fixed in Bouin's solution, and sections at a thickness of 2 to 5 microns were prepared. These were stained with hematoxylin and eosin, azancarmine, by the periodic acid-Schiff method (PAS) and in many cases by the PAS silver methenamine method.[7] In a few cases tissue was fixed in osmic acid and embedded in methacrylate; 1-micron sections were prepared and stained with methylene blue and azure blue. In most cases more than 15 glomeruli were present; when fewer than 5 glomeruli were found the tissue was considered insufficient.

Renal disease was considered to be present when persistent proteinuria or hematuria was observed. The presence of proteinuria or hematuria only at a time when the patient was febrile was not considered sufficient evidence for the diagnosis of renal involvement due to systemic lupus erythematosus.

Results

Clinical Data

Clinical data in 29 patients with renal disease in systemic lupus erythematosus are summarized in Table 1. Among the 23 patients without clinical evidence of renal disease at the time of first observation

TABLE 1. *Clinical Data on 29 Patients with Renal Disease of Systemic Lupus Erythematosus.*

PATIENT	AGE AT DIAGNOSIS	DURATION OF SYSTEMIC LUPUS ERYTHEMATOSUS	LATEST OBSERVATION					DURATION OF LATEST REMISSION	OUTCOME
			DAILY DOSE OF PREDNISONE	DURATION OF THERAPY AT THIS DOSE	PROTEINURIA	HEMATURIA	BLOOD UREA NITROGEN		
	yr.		*mg.*				*mg./100 ml.*		
G.Ga.	29	2 wk.	80	2 wk.	Present	Present	208	Still active*	Patient dead of uremia
E.M.	34	2 yr.	60	6 wk.	Present	Present	183	Still active*	Patient dead of uremia
C.D.	16	4 mo.	25	6 wk.	Present	Present	180	Still active*	Patient dead of uremia
M.L.	35	2 wk.	100	2 wk.	Present	Present	72	Still active*	Patient dead of uremia
M.C.	21	9 yr.	60	3 mo.	Present	Absent	40	Still active*	Patient dead of infection
D.Co.	37	2 yr.	60	2 mo.	Present	Absent	13	1 mo.	Patient dead of infection
G.H.	29	7 yr.	10	2½ yr.	Present	Absent	90	2½ yr.	Patient dead of pyelonephritis
J.F.	17	8 mo.	0	0	Present	Present	—	Still active*	Patient dead of systemic lupus erythematosus
N.B.	31	7 yr.	0	1 yr.	Present	Absent	18	Still active*	Patient dead of systemic lupus erythematosus
F.G.	20	2 yr.	10	4 mo.	Present	Present	—	Still active*	Patient dead of systemic lupus erythematosus
P.McC.	30	3 yr.	15	2 yr.	Present	Absent	14	Still active*	Patient dead of subarachnoid hemorrhage
M.A.	15	2½ yr.	0	6 mo.	Present	Absent	23	Still active*	Patient alive
R.S.	34	6 yr.	15	2½ yr.	Present	Absent	11	3 yr.	Patient alive
G.Gu.	31	5 yr.	15	20 mo.	Present	Absent	17	2 yr.	Patient alive
D.Cl.	63	2 yr.	5	9 mo.	Present	Absent	—	1 yr.	Patient alive
P.Ch.	38	6 yr.	10	2 mo.	Present	Present	—	Still active*	Patient alive
L.R.	24	4 yr.	10	2 mo.	Present	Absent	14	2 mo.	Patient alive
J.R.	27	4 yr.	5	2 yr.	Present	Absent	14	4 yr.	Patient alive
B.L.	21	5 yr.	0	6 mo.	Present	Absent	18	4 yr.	Patient alive
G.R.	21	10 yr.	10	20 mo.	Present	Absent	17	2 yr.	Patient alive
D.M.	11	1 yr.	10	1 mo.	Absent	Absent	14	3 mo.	Patient alive
A.M.	31	8 yr.	10	5½ yr.	Absent	Absent	16	6 yr.	Patient alive
R.A.	13	8 yr.	10	20 mo.	Absent	Absent	18	2 yr.	Patient alive
A.McK.	38	11 yr.	0	2 yr.	Absent	Absent	16	6 yr.	Patient alive
J.M.	18	2 yr.	5	1 yr.	Absent	Absent	18	18 mo.	Patient alive
J.Ro.	43	2½ yr.	20	1 yr.	Absent	Absent	16	1 yr.	Patient alive
G.DiM.	26	1 yr.	10	4 mo.	Absent	Absent	19	4 mo.	Patient alive
J.D.	16	3 yr.	10	1 yr.	Absent	Absent	18	2½ yr.	Patient alive
V.J.	37	7 yr.	10	9 mo.	Absent	Absent	16	1 yr.	Patient alive

*At time of last observation.

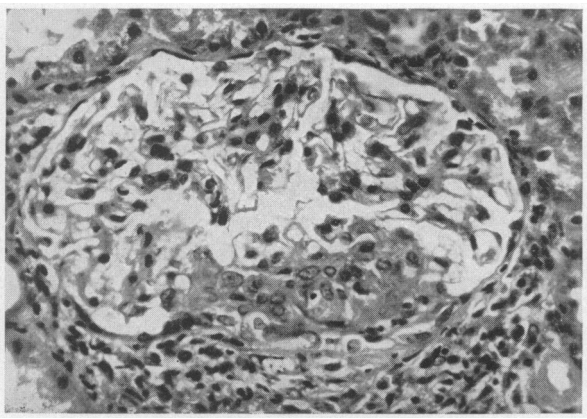

FIGURE 1. *Renal Biopsy from G.G. Obtained during Clinically Active Disease (Hematoxylin and Eosin Stain X500).*

In the lower part of the glomerulus swelling and proliferation of intracapillary cells are seen. Periglomerulitis is present.

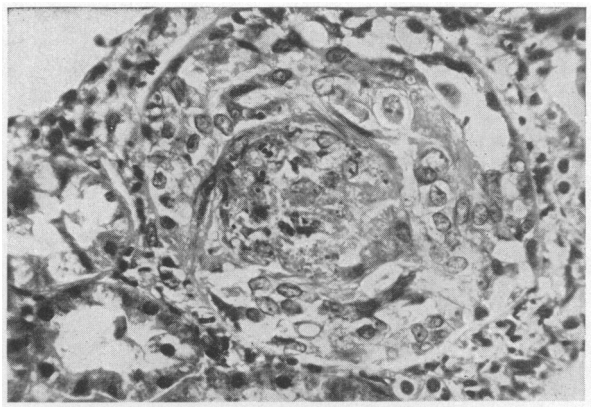

FIGURE 2. *Another Glomerulus from the Biopsy Shown in Figure 1 (Hematoxylin and Eosin Stain X500).*

There is necrosis of the glomerulus tufts, with karyorrhexis. An epithelial crescent is present.

no renal involvement was subsequently observed to develop.

A comparison of certain clinical features in the two groups is shown in Table 2. The occurrence of renal disease was independent of sex, race or age at onset. Contrary to the observations of Soffer et al.,[2] renal disease did not occur more frequently in the younger age groups. Of 30 patients with an onset under the age of thirty years 16 had renal involvement; of 22 whose disease began after that age kidney disease was present in 13.

No correlation was found between the severity of systemic lupus erythematosus as estimated by the number of organ systems involved or by the number of hospitalizations (occasioned by increased activity of the disease) and the presence or absence of renal disease. The number of patients surviving and the average duration of disease in these patients did not differ between the two groups, nor did the average duration of disease to time of death. The leading causes of death in both groups were infection and active systemic lupus erythematosus.

Pathological Findings

In the absence of clinical evidence of renal disease the kidneys showed either no pathological changes or equivocal glomerular abnormalities in the form of focal axial thickening and hypercellularity or focal basement-membrane thickening.

The pathological findings in patients with renal disease corresponded, in general, with those described by Muehrcke et al.[3] The most characteristic picture was that seen in those with clinically active systemic lupus erythematosus and consisted of focal glomerulitis (Fig. 1-3). The damaged portions of affected glomeruli showed swollen endothelial and axial cells* with vesicular nuclei, usually accompanied by endothelial and axial-cell proliferation, with narrowing or obliteration of capillaries; neutrophil infiltration was commonly present in such areas. Foci of necrosis were occasionally present and were evidenced by disappearance of normal glomerular structure, karyorrhexis and accumulation of material with the staining properties of fibrin. Classic wire loops, consisting of focal thickening of peripheral capillary loops, with brightly eosinophilic, PAS-positive material that appeared red in azancarmine stained sections, were present in some cases. Adhesions to Bowman's capsule were common, as were periglomerular infiltrates composed of lymphocytes and plasma cells and frequently containing a few eosinophils. Epithelial crescents were occasionally seen. Hematoxylin bodies were not seen in any of our specimens. The number of glomeruli involved and the extent to which any glomerulus was affected were quite variable among different patients.

An attempt was made to classify the renal lesion according to the criteria of Muehrcke et al.,[3] who have classified as lupus "glomerulitis" cases showing only glomerular involvement, without significant interstitial involvement, and as lupus "glomerulonephritis" those also showing significant interstitial and tubular involvement. It is impossible to know how closely our estimate of significant interstitial involvement corresponds to that of these authors. We did not classify as "lupus glomerulonephritis" cases showing only small, widely scattered foci of interstitial infiltration or only periglomerular inflammation. In cases classified by us as "lupus glomerulonephritis" glomerular damage was diffuse and generally rather uniform, with endothelial proliferation, some neutrophil infiltration and widespread accumulation of basement-membrane-like material with partial obliteration of glomerular capillaries. Epithelial and fibrotic crescents, interstitial inflammation and fibrosis and tubular atrophy were common. Three of these patients had necrotizing arteritis involving a few small arteries in the kidneys.

*It is now generally agreed that, in addition to epithelial cells, the glomerulus contains two types of cells — namely endothelial cells and those referred to as axial or intercapillary cells. Axial cells are located at sites of branching of capillaries and do not come in contact with the lumen. It is frequently not possible to differentiate endothelial and axial cells, and they may be referred to collectively as intracapillary cells.

TABLE 2. *Comparison of Clinical Features in Patients with and without Renal Disease of Systemic Lupus Erythematosus.*

RENAL DISEASE	NO. OF PATIENTS	SEX		RACE			AGE AT ONSET							
		MALES	FEMALES	NEGROES	WHITES	CHINESE	0-9 YR.	10-19 YR.	20-29 YR.	30-39 YR.	40-49 YR.	50-69 YR.	70-79 YR.	80-89 YR.
							no. of patients	*no. of patients*	*no. of patients*	*no. of patients*	*no. of patients*	*no. of patients*	*no. of patients*	*no. of patients*
Present	29	3	26	7	21	1	0	7	9	11	1	1	0	0
Absent	23	2	21	6	17	0	1	4	9	4	3	1	0	1
Totals	52	5	47	13	38	1	1	11	18	15	4	2	0	1

For the purposes of our analysis, the material was divided into those with or without *active* glomerular damage. The following pathological features in glomeruli were considered to be evidence of active damage: infiltration with neutrophils; proliferation and swelling of endothelial and axial cells; necrosis; and classic wire loops with the staining properties of fibrin. The following features by themselves were not considered evidence of active glomerular damage: thickening of basement membranes or accumulation of basement-membrane-like material; and focal hypercellularity (generally axial), without swelling of cells, necrosis or neutrophil infiltration.

Clinical activity of systemic lupus erythematosus and pathological evidence of active glomerular damage were determined independently by clinician and pathologist.

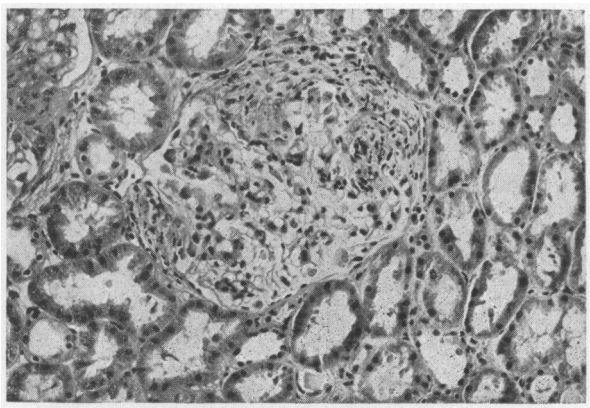

FIGURE 3. ***Renal Biopsy from R.S. during Clinically Active Disease (Hematoxylin and Eosin Stain X200).***

The glomerulus shows several areas of damage with swelling of cells, mild cellular proliferation and focal necrosis with karyorrhexis. A subsequent biopsy from this patient during remission showed only minimal focal basement-membrane thickening.

Correlation of Systemically Active Systemic Lupus Erythematosus and Anatomic Evidence of Active Glomerular Damage in Patients with Renal Involvement (Table 3)

Kidney tissue was examined in 14 patients at a time when evidence of active systemic lupus erythematosus was present in other systems. Thirteen of these had histologic evidence of active glomerular damage. On the other hand, when renal tissue was examined in 13 patients during clinical remission, 11 of whom were receiving steroids, only 1 had anatomic evidence of active glomerular damage. It appears then that active glomerular damage correlates closely with fever and evidence of clinical activity in organs other than the kidney.

The correlation of disease activity and active glomerular damage is demonstrated by comparison of serial renal-biopsy specimens obtained in individual patients (R.S. and R.A.) during remission and during clinically active disease. In each, active glomerular damage was observed during clinical activity but was not apparent during clinical remission.

TABLE 3. *Correlation of Systemically Active Systemic Lupus Erythematosus with Pathological Evidence of Active Glomerular Damage in Patients with Renal Disease.*

CLINICAL STATUS (NONRENAL)	NO. OF PATIENTS	PATHOLOGICAL DIAGNOSIS (KIDNEY)	
		ACTIVE GLOMERULAR DAMAGE*	INACTIVE
		no. of patients	*no. of patients*
Active systemic lupus erythematosus	14	13	1
Remission	13	1	12

*Necrosis, swelling & proliferation of glomerular cells, neutrophil infiltration & classic wire loops.

Clinical Manifestations of Active Glomerular Damage

Microscopic hematuria (5 or more red blood cells per high-power field in the spun sediment) was pres-

TABLE 2 *(Concluded).*

RENAL DISEASE	AVERAGE NO. OF ORGAN SYSTEMS INVOLVED/ PATIENT	AVERAGE NO. OF ADMISSIONS/ PATIENT FOR ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS	SURVIVING PATIENTS			DEAD PATIENTS			CAUSE OF DEATH					
			NUMBER	AVERAGE DURATION*	RANGE OF SURVIVAL	NUMBER	AVERAGE DURATION FROM ONSET	RANGE OF DURATION BEFORE DEATH*	INFECTION	ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS	SUBARACHNOID HEMORRHAGE	PULMONARY EMBOLISM	CHRONIC PYELONEPHRITIS	UREMIA DUE TO RENAL DISEASE OF SYSTEMIC LUPUS ERYTHEMATOSUS
				yr.	*yr.*		*yr.*	*yr.*	*no. of patients*	*no. of patients*	*no. of patients*	*no. of patients*	*no. of patients*	*no. of patients*
Present	7.6	3.4	18	5.4	1-11	11	4 11/12	4 mo.-15 yr.	2	3	1	0	1	4
Absent	7.0	3.6	14	6.3	1 1/2-12	9	5	4 mo.-13 yr.	4	4	0	1	0	0
Totals			32			20			6	7	1	1	1	4

*From onset of symptoms.

ent in 11 of 14 patients with pathological evidence of active glomerular damage. Of 13 patients without active glomerular damage only 2 had hematuria, both of whom had other possible causes of hematuria (renal tuberculosis in M.C. and acute pyelonephritis in G.H.). Proteinuria was not always an indication of active glomerular damage since it was found in 8 of 13 patients with anatomically inactive glomerular disease.

Outcome of Patients with Renal Disease (Table 1)

Persistent renal disease. Twenty of the 29 patients with clinical evidence of renal disease have had persistent renal involvement as evidenced by continuing proteinuria for periods ranging from two weeks to ten years.

Renal insufficiency, with blood urea nitrogen in excess of 20 mg. per 100 ml., was observed in 7 of the 20 patients, 4 of whom have died of uremia. Death due to renal insufficiency occurred within four months of the time of diagnosis of systemic lupus erythematosus in 3 of these 4 patients (G.Ga., C.D. and M.L.) and after two years in the other (E.M.). Clinical evidence of lupus activity in other systems was not completely controlled by the dosage of steroid therapy employed in these 4 patients. Active glomerular damage was severe and diffuse and was accompanied by interstitial inflammation and tubular abnormalities, and the pathological picture was consistent with "lupus glomerulonephritis" as described by Pollak et al.[4] Three of the 4 patients already had elevation of blood urea nitrogen at the time of the first observation, and active, progressive renal disease was present throughout the course. The fourth patient (E.M.), who survived for two years, had systemically active systemic lupus erythematosus and progressive renal disease during the last six months of the course. The remaining 3 patients, in whom renal insufficiency developed, did not die of renal disease due to systemic lupus erythematosus. After nine years of disease, M.C. died of an infection due to a hemolytic streptococcus with a blood urea nitrogen of 40 mg. per 100 ml. and during a third episode of the nephrotic syndrome. The left kidney had been resected because of renal tuberculosis five years before death. The surgical specimen showed very extensive tuberculous pyelonephritis. Diffuse, mild, fairly uniform thickening of glomerular basement membranes, as well as mild, slightly irregular hypercellularity, was present. At autopsy the right kidney showed diffuse glomerular abnormalities characterized by mild basement-membrane thickening, moderate irregular accumulation of basement-membrane-like material and mild, irregular glomerular hypercellularity. Scattered tubules were calcified. Interstitial inflammation was not present. M.A., at the time of last observation, had systemically active systemic lupus erythematosus and minimal elevation of the blood urea nitrogen after a six-month period of remission, during which steroids had not been administered. G.H. died of uremia due to chronic pyelonephritis, which was demonstrated two and a half years before death on renal biopsy and confirmed at autopsy. Remission of systemic lupus erythematosus had been maintained for five years before death.

The 13 remaining patients with persistent proteinuria were observed for periods ranging from two months to ten years, without the development of renal insufficiency. In these patients with persistent proteinuria and systemically inactive systemic lupus erythematosus active glomerular damage was not found in renal biopsies although basement-membrane thickening, either focal or diffuse, was present. Five of these patients died of other causes, 3 of active systemic lupus erythematosus, 1 of infection (miliary tuberculosis), and 1 of spontaneous subarachnoid hemorrhage.

Remission of renal disease. Of the 29 patients who initially had clinical evidence of renal disease 9 had no urinary abnormalities at time of the last observation. Proteinuria persisted for two months to four years in these patients before clinical remission of the renal disease occurred. Biopsies, performed in 2 of these patients after disappearance of urinary abnormalities, revealed only equivocal focal increase in basement-membrane-like material.

The current clinical status of the 18 surviving patients from the group of 29 who had evidence of renal involvement at the onset of the disease is summarized in Table 4.

Outcome in relation to initial severity of renal disease. Ten patients had elevation of blood urea nitrogen at the onset. Included in this group are the 4 described above who died of renal disease due to systemic lupus erythematosus (G.Ga., E.M., C.D. and M.L.) and another (G.H.), who died of chronic pyelonephritis. Five patients (G.DiM., J.D., L.R., J.R. and A.M.), who had azotemia at onset, are still alive one year, three years, four years, four years and eight years later, without evidence of renal insufficiency. Biopsy during remission was done in only 1 of these patients (A.M.) and showed only equivocal focal basement-membrane thickening. All had complete suppression of systemically active systemic lupus erythematosus within two months of onset after administration of steroids. Two (L.R. and J.R.) have only proteinuria at the present time, and the other 3 (A.M., G.DiM. and J.D.) have no clinical evidence of renal disease. All 5 surviving patients have been continuously on minimal daily corticosteroid therapy.

TABLE 4. *Clinical Renal Status of 18 Surviving Patients Who Had Renal Disease at Onset of Systemic Lupus Erythematosus.*

PRESENT STATUS	DURATION OF DISEASE			
	<3 YR.	3-7 YR.	>7 YR.	TOTALS
	no. of patients	*no. of patients*	*no. of patients*	
Proteinuria	2	6	1	9
Azotemia	1*	0	0	1*
No clinical evidence of renal disease	4	2	3	9
Totals	6	8	4	18

*This patient included among those with proteinuria.

Nephrotic Syndrome

In 7 patients the nephrotic syndrome developed as a manifestation of renal disease due to systemic lupus erythematosus. Six had systemically active disease at the time the nephrotic syndrome was present; 3 of these had coexistent renal insufficiency and died of uremia within four months (G.Ga., C.D. and M.L.). In 3 other patients with the nephrotic syndrome and systemically active systemic lupus erythematosus remission was induced with steroid therapy. Two are alive after seven and nine years (G.R. and A.M.). The third (M.C.) died of infection nine years after onset of systemic lupus erythematosus and during a third episode of the nephrotic syndrome.

In the seventh patient (B.L.) the nephrotic syndrome developed two years after diagnosis of systemic lupus erythematosus at a time when the disease was otherwise inactive. Biopsy gave no evidence of active glomerular damage but showed uniform thickening of the basement membrane. Remission of the nephrotic syndrome was induced with steroids within two months, and the patient is now alive after five years of continuously inactive systemic lupus erythematosus, with persistent minimal proteinuria as the sole manifestation of renal disease. Serial renal biopsies taken two and four years after remission of the nephrotic syndrome have shown diffuse and uniform thickening of glomerular basement membranes that are unchanged from the initial findings.

DISCUSSION

The present study of patients with renal disease in systemic lupus erythematosus demonstrates that the prognosis is not so poor as previous reports suggest.[1,2] Treatment directed toward control of other manifestations of systemic lupus erythematosus was accompanied by prolonged remission of the renal lesion in the majority of our patients.

Renal disease was observed in 56 per cent of the patients, and in all it was present at the time of first observation. This is in agreement with the findings of Soffer et al.[2] It can be concluded that in patients who have no evidence of renal involvement initially renal disease will probably not develop later in the course of systemic lupus erythematosus. This is consistent with the observation that the pattern of involvement of other systems in systemic lupus erythematosus tends to be repetitive for individual patients.[8]

With 1 exception active glomerular damage was observed only in patients who had evidence of active systemic lupus erythematosus in other systems. The basic alteration seen during periods of lupus activity consisted of focal glomerulitis, characterized by swelling and proliferation of endothelial and axial cells, frequently with neutrophil infiltration, and often with foci of necrosis and deposits of fibrinoid. Acute periglomerulitis was a frequent finding. In one respect our findings differ from those of others — namely, in the complete absence of hematoxylin bodies in our material. We have no explanation for our failure to find these structures. The clinical manifestations of active glomerular disease were proteinuria and hematuria in the great majority of patients, and patients with more severe, active glomerular alterations had, in addition, varying degrees of renal insufficiency, usually with the nephrotic syndrome. Hematuria was not observed in the absence of active glomerular damage. The presence of hematuria, therefore, is clinical

evidence of active glomerular disease and seems an indication for increased dosage of corticosteroids.

Treatment with steroids in dosage sufficient to control activity of systemic lupus erythematosus in systems other than the kidney has proved adequate for control of the renal disease in the majority of patients. Anatomic evidence of active glomerular damage disappeared, and hematuria subsided, leaving only proteinuria. During remission the glomeruli may appear normal or may show signs of residual abnormalities in the form of focal basement-membrane thickening or a focal, axial increase in basement-membrane-like material with increased numbers of axial cells. With repeated episodes of lupus activity, active glomerular damage reappears, but with control of the disease, progressive glomerular sclerosis does not occur. The usual course of renal disease in systemic lupus erythematosus, with its exacerbations and remissions, is in striking contrast to the sequence of events after acute poststreptococcal glomerulonephritis, in which continuous regression of initial glomerular damage is usual.[9]

In most of our patients mild proteinuria persisted during clinical remission on minimal doses of corticosteroids, but evidence of progressive renal disease did not appear even after many years. In some proteinuria subsided completely after months or years of continuous sustained remission induced by corticosteroids. The results suggest that treatment of active systemic lupus erythematosus by the minimal doses required to suppress systemic manifestations is adequate to halt the progression of renal disease and that prolonged administration of large doses of corticosteroids is not indicated when proteinuria is the sole manifestation of renal involvement. On the other hand, the data suggest that the presence of the nephrotic syndrome, which occurs only rarely in the absence of active systemic lupus erythematosus in the kidney or other systems, should be treated with larger doses of steroids, with the clinical objective of diminishing the degree of proteinuria.

Pollak et al.[4] have applied the term "lupus glomerulonephritis" to characterize "a proliferative and/or membranous lesion of the glomeruli, associated with tubular and interstitial tissue changes." They have stressed the poor prognosis in such patients in contrast to those with "lupus glomerulitis" in whom tubular and interstitial changes were absent and the glomerular lesions were generally milder. These authors have stated that the administration of prednisone in doses of 40 mg. per day for six months may favorably alter the course in patients with "lupus glomerulonephritis." They imply that corticosteroids in doses just adequate to control activity of systemic lupus erythematosus in other systems is not sufficient to halt the progression of "lupus glomerulonephritis." In 9 of our patients the anatomic picture appeared to correspond to that described as "lupus glomerulonephritis." Four of the 9 died of uremia within two weeks to two years of the time of diagnosis (G.Ga., E.M., C.D. and M.L.). In none of these was clinical activity of systemic lupus erythematosus in other systems suppressed by the dosage of steroids administered. Although prednisone was given in doses ranging from 25 to 100 mg. per day during the last few weeks before death our observations do not permit us to conclude whether even larger doses of steroids might have altered the course in these patients. Two other patients, J.F. and P.McC., died of active systemic lupus erythematosus and subarachnoid hemorrhage respectively, not of uremia, and were found to have the changes of "lupus glomerulonephritis" at autopsy. Both patients had evidence of active systemic lupus erythematosus in other systems at the time of death. In the 3 remaining patients, G.Gu., L.R. and J.R., clinical remission of systemic lupus erythematosus and of "lupus glomerulonephritis" was induced and then sustained by doses of 5 to 15 mg., with survival now exceeding four years. In 2 of these 3 surviving patients the glomerular involvement, though severe, was focal within and among glomeruli, and the cases were classified as "lupus glomerulonephritis," according to the definition of Pollak et al.,[4] because of conspicuous interstitial inflammation and tubular atrophy. It is apparent, then, that we have observed remission in only 1 of 7 patients with diffuse and severe glomerular lesions, characterized mainly by proliferation and accumulation of basement-membrane-like material tending to involve the entire glomerulus. This suggests that *diffuse* involvement of glomeruli is of more ominous prognostic significance than "lupus glomerulonephritis," in which interstitial inflammation and tubular changes may be present with only *focal* glomerular involvement. With severe diffuse glomerular involvement interstitial inflammation and tubular atrophy are almost invariably present as well, but these changes are commonly seen also in the absence of diffuse glomerular abnormalities and probably have no particular prognostic significance.

In accordance with the observations of others[2,3] the nephrotic syndrome occurred in approximately 15 per cent of our patients. It was almost invariably associated with active glomerular damage, but the prognosis was not uniformly poor. Although half had rapidly progressive renal failure the others entered sustained periods of remission and are alive five to nine years after the onset of systemic lupus erythematosus.

These observations indicate that the more commonly occurring renal lesion of systemic lupus erythematosus (glomerulitis) may be controlled by treatment that is adequate to cause remission of activity in other systems. However, in a minority of patients, more severe and diffuse glomerular involvement occurs. This may reflect simply a severe form of lupus glomerulitis that is more difficult or impossible to control with steroids. Alternatively, severe diffuse glomerular involvement may represent a process dif-

fering in some fundamental way from focal glomerulitis and less susceptible to the action of steroids.

Summary

A study of the incidence and characteristics of renal disease in 52 patients with systemic lupus erythematosus is presented.

Renal disease occurred in 29 of the 52 patients.

The presence of active glomerular damage correlated closely with activity of systemic lupus erythematosus in other systems.

In the majority of patients with renal disease in systemic lupus erythematosus the glomerular lesion was a focal one, subsiding when adrenal corticosteroids were given in doses sufficient to suppress activity in other systems.

In a minority of patients the glomerular lesions were severe and diffuse, and the renal disease usually progressed to fatal renal insufficiency.

Infections and active systemic lupus erythematosus were more frequent causes of death than renal disease in the present series.

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CARCINOMA OF THE LUNG WITH INAPPROPRIATE ANTIDIURESIS*

Demonstration of Antidiuretic-Hormone-Like Activity in Tumor Extract

THOMAS T. AMATRUDA, JR., M.D.,† PATRICK J. MULROW, M.D.,‡ JOHN C. GALLAGHER, M.D.,§ AND WILBUR H. SAWYER, M.D., PH.D.¶

WEST HAVEN, CONNECTICUT, AND NEW YORK, NEW YORK

THE association of carcinoma of the lung with hyponatremia and renal sodium loss has been reported on several occasions. Schwartz et al.[1] first demonstrated the presence of inappropriate antidiuresis in patients with this syndrome and suggested that it was due to inappropriate secretion of antidiuretic hormone. There have been no reports of elevated levels of vasopressin in the blood of such patients. Even in maximal antidiuresis, however, peripheral blood concentrations of vasopressin could easily escape detection by presently available methods for extraction and biologic assay. The pathogenesis of the syndrome has been obscure, but a neurogenic basis due to involvement of the vagus nerves by tumor has been postulated. The present report is a study of a patient with this syndrome resulting from oat-cell carcinoma of the lung. The tumor exhibited antidiuretic activity when tested by a biologic assay, raising the possibility that the inappropriate antidiuresis in this patient was due to a substance elaborated by the tumor.

*From the Veterans Administration Hospital, West Haven, the Department of Internal Medicine, Yale University School of Medicine, and the Department of Pharmacology, Columbia University College of Physicians and Surgeons, New York.

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†Chief, Medical Service, Veterans Administration Hospital, West Haven; assistant professor of medicine, Yale University School of Medicine.

‡Assistant professor of medicine, Yale University School of Medicine; formerly, clinical investigator in medicine, Veterans Administration Hospital, West Haven.

§Formerly, resident in pathology, Veterans Administration Hospital, West Haven.

¶Associate professor of pharmacology, Columbia University College of Physicians and Surgeons.

Case Report

R.L. (V.A.H. 2069), a 67-year-old retired steam fitter, was admitted to the Veterans Administration Hospital, West Haven, Connecticut for the 1st time on August 28, 1959. He related a long history of urinary frequency and obstructive symptoms due to prostatism. He also described a chronic cough of many years' duration, productive of small amounts of clear sputum, and he had smoked 1½ packages of cigarettes daily for more than 50 years.

Physical examination revealed an alert man and was unremarkable except for a large, symmetrical prostate gland.

The temperature was 98°F., and the pulse 84. The blood pressure was 165/80.

The hemoglobin was 16.5 gm. per 100 ml., and the hematocrit 50 per cent. The urinary sediment contained a few red cells, white cells and bacteria. The blood urea nitrogen was 18 mg. per 100 ml.; the serum electrolytes were not measured. X-ray study of the chest was within normal limits (even in retrospect), and intravenous pyelograms revealed good function bilaterally. Phenolsulfonphthalein excretion was 67 per cent in 2 hours. A residual urine of 300 ml. was demonstrated, and urine culture grew a few colonies of coliform bacteria.

A partial suprapubic prostatectomy was carried out without difficulty on September 15, 1959, and pathological examination revealed benign prostatic hypertrophy. The patient had an uneventful postoperative course and was discharged on October 5, 1959. However, he continued to