Renal

THE KIDNEY IN SYSTEMIC LUPUS ERYTHEMATOSUS

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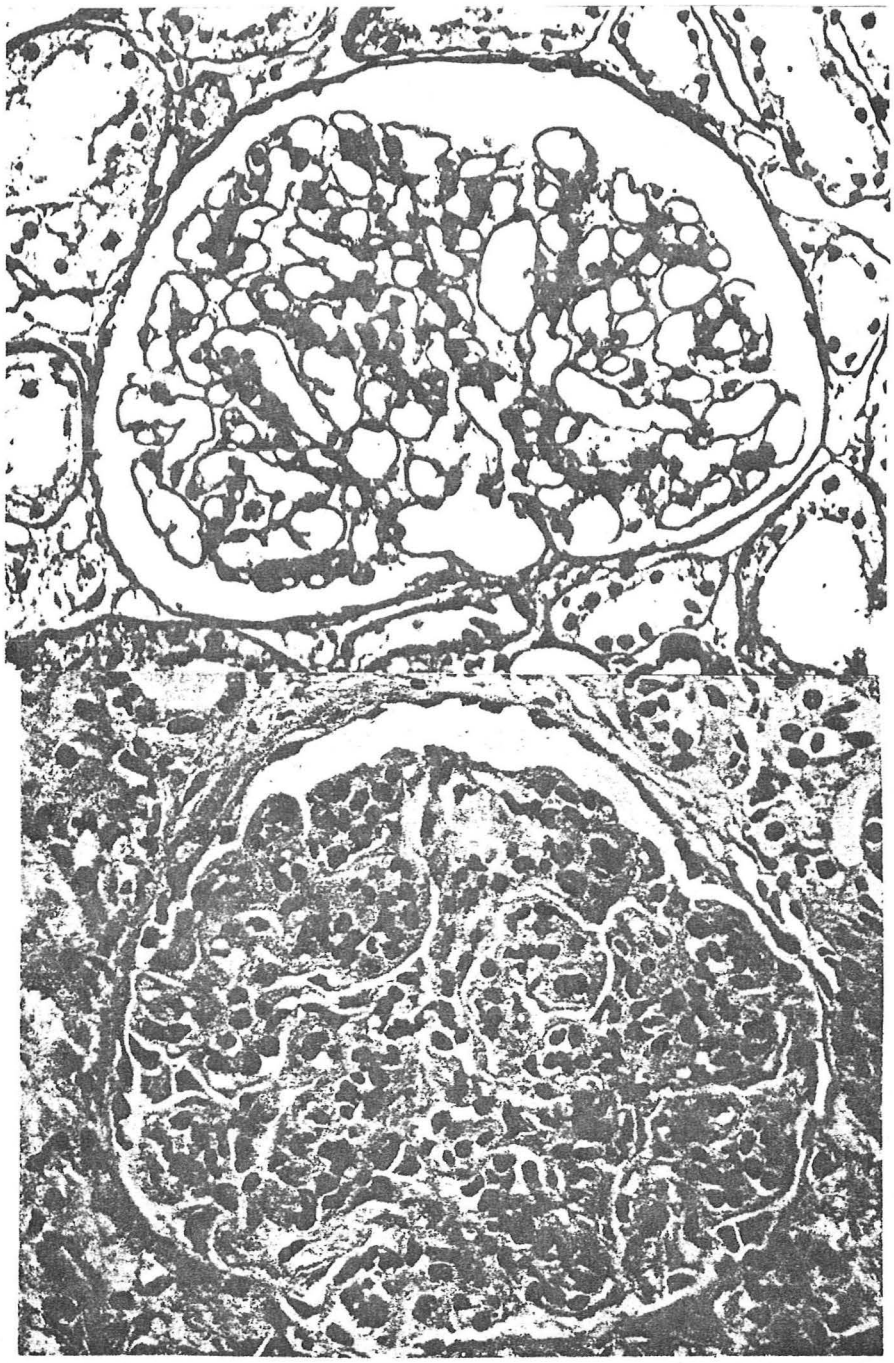

Omnia mutantur nos et mutamur in illis. Lothaire I

All things change and we change with them.

HISTORICAL CONSIDERATIONS

In 1872 Kaposi (1) stressed the fact that lupus was more than just a dermatological disease, but that other organ systems could be involved. Subsequently Keith and Rowntree in 1922 (2) stressed the renal complications of SLE from a clinical study of four cases - two of whom died. Two years later Libman and Sacks (3) described sterile vegetations on the heart valves in four patients with SLE - three of whom had renal disease at autopsy. One decade later Bachs, Klemperer and Schifrin gave detailed autopsy findings in 23 patients with SLE (4). These investigators described glomerular lesions in 18 patients with "wire loops" in 13. They commented that these "wire loops" resembled the lesions "seen in horses immunized by repeated intravenous injections of live bacteria, especially of the pneumococcus-streptococcus group". It is of interest to note that when this paper was presented, a Dr. Wadsworth, who was present at the discussion, commented that horses immunized in such a manner not infrequently developed bacterial endocarditis. We now know that renal lesions in bacterial endocarditis are due to immune complex deposition.

The next major historical development in SLE was the discovery of the "L.E." cell by Hargraves and his colleagues (5). The significance of this finding lies in the fact that subsequently classification of patients with certain clinical features of SLE could be documented as SLE by the presence of a positive L.E. test. This and subsequent serological tests to be discussed are responsible for the apparent (but not real) increase in the incidence of SLE since 1950.

The 1950's and early 1960's are remarkable for the production of classical clinical and pathological studies of SLE and SLE nephritis. In the major review of SLE from Johns Hopkins (6), a detailed clinical analysis of 138 cases and review of the literature were presented. These authors found clinical evidence for renal disease in 65% of their patients. Similarly, in the other major study, which eminated from The University of Illinois (7), clinical evidence for renal involvement was found in 80-90% of patients. The latter study was significant for two reasons. First it used the newly developed technique of renal biopsy (8) to gain valuable clinical information, and second, it represented the first major attempt at histological classification of the renal disease of SLE by light microscopy. Thirty-three patients were biopsied. Eleven had normal appearing biopsies (three absolutely normal, eight with minimal glomerular changes), ten had glomerulitis, and twelve had glomerulonephritis. Seven patients out of the last group died of uremia while all of the other patients survived without the development of uremia. In agreement with these two major studies, other publications at this time discovered a clinical and/or pathological incidence of renal disease in SLE from 59-91% (9-15).

TABLE I

HISTORICAL CONSIDERATIONS

1.	Kaposi	1872	Systemic component of lupus
2.	Keith & Rowntree	1922	Stressed renal involvement in SLE
3.	Libman & Sacks	1924	Sterile endocarditis and renal disease in SLE
4.	Baehr, Klemperer & Schifrin	1935	Detailed autopsy of SLE describing glomerular "wire loop"
5.	Hargraves et al.	1948	L.E. cell
6.	Harvey et al.	1954	Detailed clinical study of SLE
7.	Kark & Muehrcke	1954	Renal biopsy
8.	Muehrcke	1957	Histological classification of renal disease in SLE
9.	Dixon et al.	1961	Immune complex nephritis
10.	Tan et al.	1966	Serum DNA and anti-DNA
11.	Schur & Sandson	1968	Relationship between anti-DNA, complement and clinical activity
12.	Koffler	1969	Pattern of immunoglobulin and complement deposition in glomeruli
13.	Koffler et al and Krishnan & Kaplan	1967	Glomerular eluates demonstrating anti-DNA antibody
14.	Helyer & colleagues	1963	NZB/NZW mice

The 1960's and early 1970's saw the expansion of our understanding of immunity, autoimmunity, and the role of immune complexes in the renal disease of SLE. The classic paper of Dixon et al (16), describing the pathogenesis of immune complex nephritis in rabbits, stressed the significance of the quantitative relationship between antigen and antibody in serum. (Subacute and chronic glomerulonephritis developed in animals whose circulation contained antigen and antibody near either slight antigen or slight antibody excess. It is now well recognized that SLE renal diseases (at least some types) are prime examples of immune complex nephritis (17). Serologic studies demonstrated that the appearance of several kinds of humoral antibodies and depression of serum complement were associated with clinical activity of SLE in patients with and without renal disease (18, 19). In addition, in patients without clinical evidence of renal disease, the finding of immune complexes in the glomerular mesangium (20) led to the postulate that the mesangium acts as the first line of defense against injury and is delegated the responsibility of phagocytying these complexes. Finally, eluates from glomeruli recovered antibodies to native-DNA and other nucleoproteins (21, 22).

TABLE II

RENAL INVOLVEMENT IN SLE - EARLY STUDIES

	Author	Year	Number Of Patients	% Renal Involvement	
1.	Harvey et al.	1954	105	65	(C)
2.	Muehrcke et al.	1957	33	66	(C+P)
3.	Montgomery and McCreight	1949	132	59	(C)
4.	Klemperer		45	91	(A)
5.	Shearn and Pirofsky	1952	34	62	(C)
6.	Jessar et al.	1953	44	77	(C)
7.	Soffer et al.	1961	90	62	(C)
8.	Wilson et al.	1963	52	67	(C+P)
9.	Rothfield et al.	1963	52	56	(C+P+A)

C = Clinical P = Pathological (biopsy) A = Autopsy

Of major significance was the development of a strain of mouse, hybrid of New Zealand white and black mice (NZB/NZW F_1), that has autoimmune phenomena similar to human lupus and in addition universally develop glomerulonephritis and chronic renal failure (23, 24). These mice have served two important purposes--1) to further investigate the immunopathogenesis of SLE and SLE renal disease and 2) to serve as a treatment model for the human disease. A critical discussion of these developments in immunopathogenesis and experimental models of SLE renal disease are beyond the scope of this presentation. However, certain aspects of these developments are pertinent with respect to aiding in the clinical diagnosis of SLE nephritis, monitoring treatment, and forming rationale for therapy. Thus they will be considered subsequently.

"MODERN" ERA OF SLE AND THE KIDNEY

The major theme of the "modern" era of lupus renal disease is histological classification into subsets that can be differentiated with respect to prognosis, requirements for therapy, response to therapy, and possibly even immunopathophysiology. Included in histological classification is examination of tissue by light microscopy, electron microscopy, and immunofluorescence. To be sure, the modern era has continued to see major developments in understanding various immunological abnormalities in SLE (the roles of T lymphocytes and their subpopulations and B lymphocytes), but with respect to the kidneys, diagnosis, treatment, treatment surveilence, and prognosis have centered around histologically defined subsets.

Baldwin and his coworkers set the theme for the current era in 1970 (25) when they presented three histologic forms of lupus nephritis in a series of 52 patients. Table III presents these authors' classification scheme. Patients were classified as having focal or diffuse proliferative glomerulonephritis or membranous lupus nephritis. It should be noted that all of these patients had clinical evidence of renal disease on the basis of urinalysis or the presence of azotemia. As can be seen from Table IV, the development of azotemia and death was very highly correlated with the histological subset.

Although it was not the purpose of their study to evaluate therapy, all but two patients in this series received steroids in doses to control systemic manifestations of lupus. If clinical renal disease did not remit along with the systemic manifestations, prednisone, 40-80 mg/day, was given. Generally speaking, although doses and duration of treatment were not presented, the authors found: 1) no progression of renal disease clinically or on repeat biopsy (only two patients) without the requirement of high dose steroids in patients with focal proliferative. However persistent or intermittent hematuria or proteinuria was present in all but two patients. 2)

Short term partial clinical remission in 50% with most relapsing and progressing to end stage renal disease in the group of patients with diffuse proliferative. In ten patients with repeat biopsy or autopsy no histologic remission was seen. 3) Persistent proteinuria and nephrotic syndrome (with rare sustained remission) and gradual development of renal failure in spite of high dose steroids in patients with membranous lupus. Repeat tissue in five showed one complete histological remission and one "progression" to diffuse proliferative.

TABLE III

CLASSIFICATION OF LUPUS NEPHRITIS - Baldwin et al 1970

Focal Proliferative Glomerulonephritis	*(14)*	Mesangial and endothelial cell proliferation in portions of some glomeruli. Lesions of activity (neutrophils, nuclear fragmentation, capsular adhesions) may be present. Tubules and interstitium mostly normal. EM and IF not described.
Diffuse Proliferative Glomerulonephritis	(24)	Same as focal but involvement of most-all glomeruli and more complete involvement of each glomerulus. Crescents present. Tubular and interstitial involvement usual. Immunofluorescence -gamma globulin and complement inmesangium and capillary loops. EM - deposits correlating with IF including subendothelial.
Membranous Lupus Nephritis	(14)	Little or no hypercellularity. Uniform basement membrane thickening. IF -gamma globulin and complement. EM -deposits - subepithelial.

From the data of Baldwin et al (25) and parts of their discussion, several major questions can be asked about lupus renal disease. 1) Does renal biopsy and histological classification provide useful prognostic, etiologic, and therapeutic information? 2) Are histological subsets discrete entitites or do they represent various stages of a single process? 3) Is clinical deterioration or improvement in renal involvement associated with progression or transformation or regression of the histological picture? 4) Does therapy (and what kind of therapy) affect the clinical and/or histologic expression of the renal disease? 5) Are there alternative or adjunctive tests (other than biopsy) that can either predict histology or

determine treatment decisions? The major portion of work in lupus renal disease during the past decade and thus the bulk of the rest of this discussion address these questions.

TABLE IV

OUTCOME ACCORDING TO HISTOLOGY - Baldwin et al 1970

	Alive		Dead	
	Normal Renal Function	Azotemia	Uremic	Non-renal
Focal Proliferative	8 (6-164 mo)*	1 (68 mo)	0	5 (5-60 mo)
Diffuse Proliferative	4 (24-120 mo)	3 (6-96 mo)	9 (2-60 mo)	8† (6-54 mo)
Membranous Lupus	6 (30-144 mo)	3 (8-42 mo)	3 (1-90 mo)	2† (24, 108)

*After onset of renal disease

†Azotemic at death

MAGNITUDE OF THE PROBLEM

Two recent population studies listed on Table IV (26, 27) provide some information about the incidence and prevalence of SLE in the U.S. In addition, one study (27) provides information on the prevalence of clinical renal disease. Nobrega (26) found the annual incidence of SLE in Rochester, Minnesota was 6.4/100,000 with a prevalence of 1/2,400. Fessel (27), studying the Kaiser Permanente population, found an annual incidence of 7.6 new cases per 100,000 population and a prevalence of 1/1969. Interestingly the prevalence in black women aged 15-64 was 1/245. These studies would predict that roughly 92,000 patients currently have SLE in the U.S.

In contrast to the already presented older studies depicting the prevalence of clinical renal disease in lupus at roughly 50-60%, Fessel (27) found that only 10/64 (16%) patients reviewed in 1973 had evidence of renal disease. The reason for this discrepancy is not clear but may be related to the fact that most clinical publications on SLE come from referral centers which are expected to see more severe cases. It is possible that with the serological aids to diagnosis, more recent series of patients might have a lower prevalence of renal disease. However, in an ongoing multicenter study of

lupus recently abstracted (28) the prevalence of renal disease based on serum creatinine (creat. >1.3 mg%) was 27% and based on semiquantitative proteinuria (2+ or greater on dipstick) was 45%. This study included 1103 patients entered from nine university-affiliated centers chosen to include a spectrus of geographic, racial, and socioeconomic factors. Details are not yet available to determine the true prevalence of renal disease in this large group of lupus patients.

TABLE V

INCIDENCE AND PREVALENCE OF SLE

	Annual Incidence SLE	Prevalence SLE	Clinical Renal Disease
Nobrega (1965)	6.4/100,000	1/2400	
Fessel (1974)	7.6/100,000	1/1969	16%
Current Calculation	14,000	92,000	15-46,000

WHO CLASSIFICATION

Although the early work of Baldwin et al (25) set the theme for the current approach to renal lupus, three major subsequent developments have necessitated reorganization of the histological classification. First, the routine use of the electron microscope has allowed detection of pathology not seen under light microscopy. As will be discussed, study of tissues from patients with minimal or no clinical evidence of renal disease has disclosed a new histological subset. Second, as will also be discussed, electron microscopic localization of glomerular deposits has appeared to provide a correlation between deposit site and clinical course. Third, mounting evidence for significant change in a given patient's histology with disease activity or treatment has necessitated the development of well defined reasonably narrow histologic subsets.

The World Health Organization has outlined a classification scheme depicted in Table VI.

TABLE VI

WORLD HEALTH ORGANIZATION CLASSIFICATION

Class I	Normal Kidneys	No detectable changes by LM, EM, IF
Class II	Mesangial Changes	
IIA	Minimal Alteration	Normal LM. Mesangial deposits of immunoglobulin and complement by IF. Mesangial deposits by EM.
IIB	Mesangial Glomerulitis	Same as IIA but also mesangial hypercellularity (more than 3 cells per mesangial area away from vascular pole in 2-4 μm sections) and/or increased mesangial matrix. Minimal tubular or interstitial changes.
Class III	Focal and segmental proliferative glomerulonephritis	In addition to any finding(s) in Class II, less than 50% of glomeruli involved with focal areas of intra- and extracapillary cell proliferation, necrosis, karyorrhexis, and leukocytic infiltration. EM and IF can show subendothelial as well as mesangial deposits. Tubular and interstitial changes usually focal.
Class IV	Diffuse proliferative glomerulonephritis	Similar to Class III but involving more glomerular surface area and greater than 50% of the glomeruli. IF and EM often show abundant *subendothelial* deposits. Interstitial involvement more marked. Membranoproliferative variant has prominent mesangial cell proliferation and capillary wall thickening by mesangial extensions.
Class V	Membranous Glomerulonephritis	No mesangial, endothelial or epithelial cell proliferation. Capillary walls diffusely and uniformly thickened. IF and EM show mesangial and *subepithelial* deposits. Minimal interstitial involvement like Class II.

It should be noted that in addition to these subsets, there are certain reasonably well accepted pathological hallmarks of activity. For instance, segmental necrosis, karyorrhexis, wire loops, hematoxyphil bodies, epithelial crescents, interstitial accumulation of lymphocytes and plasma cells, and probably subendothelial deposits are indicative of activity while glomerular sclerosis, fibrous crescents, interstitial fibrosis and probably glomerular basement membrane thickening and subepithelial deposits are indicative of inactivity or "healing".

RELATIONSHIP BETWEEN CLINICAL PRESENTATION AND CLASSIFICATION, TRANSFORMATION AND SIGNIFICANCE OF LOCATION AND AMOUNT OF DEPOSITS.

Excluding for the moment the questions of treatment and correlation of serological events with clinical and renal histologic course, it is of interest to review recent reports of patients with lupus renal disease and examine the questions of 1) the relationship between clinical presentation and histologic classification, 2) transformation (in this presentation transformation is meant to describe a change from one histologic class to another--better or worse--and is not meant to imply that this change is either evolutionary or a true transformation), and 3) the significance of the location and amount of deposits in the kidney.

RELATIONSHIP BETWEEN CLINICAL PRESENTATION AND HISTOLOGIC CLASSIFICATION

The histologic class and clinical presentation at biopsy is presented in Table VII for two recently published series of patients (30, 31). While these studies differed in the proportion of patients in each subset, it is apparent that several general statements can be made. First, proteinuria and, although not shown in the table, hematuria with the absence of the nephrotic syndrome is characteristic of Class II lesions. Azotemia is uncommon and mild with rare progression to uremia in Class II. In Class III proteinuria is the rule but nephrotic syndrome and azotemia are not common. Uremic deaths occur in a very few. Class IV patients always have proteinuria, usually in the nephrotic range. In addition azotemia is present in most at presentation and uremia is the most common cause of death. Finally, Class V patients all have proteinuria and most are nephrotic. In these patients azotemia occurs in the minority and uremic deaths are uncommon.

TABLE VII

HISTOLOGIC CLASS AND CLINICAL PRESENTATION AT BIOPSY

Series	# Of Patients		Proteinuria	Nephrotic*	Azotemia†	Deaths	Uremic Deaths
Baldwin (1977)	Total	88					
	IIa IIb	12	8	0	2	0	0
	III	12	12	1	2	3	0
	IV	44	44	41	36	28	18
	V	24	23	16	6	9	1
Appel (1978)	Total	55					
	IIa	6	3	0	1	1	0
	IIb	16	12	0	1	5	0
	III	15	15	3	3	5	3
	IV	9	9	5	4	3	1
	V	10	10	10	1	4	1

*>3 gm proteinuria/24 hrs.

†BUN >25 or creat >1.2 mg%.

Although the studies in Table VII are appropriate examples of the relationship between histology and presentation, certain patients are exceptions to this scheme. Of major potential importance is the patient with a normal urinalysis, no significant proteinuria, and normal BUN and creatinine or creatinine clearance. In nine studies (7, 30-37) (most of which were designed specifically to select out this kind of patient) depicted in Table VIII are listed 86 patients who at the time of biopsy had unequivocally normal urine sediment, normal 24 hr urine protein excretion, and normal clearance or serum creatinine. In 78% of these patients Class II or III histology was found, 2% had Class V, and 20% had Class IV. Although follow-up data is incomplete, only one of the 17 Class IV patients has progressed to uremia and died. In addition, even though serologic tests were not presented in all patients, only 15 of 67 (22%) patients had normal complements and anti-DNA titer or binding capacity. However, these studies clearly document that patients with SLE can have significant renal pathology without clinical evidence. Thus if one were inclined to make therapeutic decisions on the basis of renal histology, all patients would require renal biopsy.

The original series of Baldwin (25) found an incidence of focal glomerulonephritis of 27%, of diffuse proliferative glomerulonephritis of 46%, and of membranous lupus of 22%. Utilizing the WHO classification, and occasionally converting the authors' classification, Table IX shows the relative incidence of the various histologic classes of lupus renal disease seen on initial biopsy. Although there is an occasional wide spread within a given class, it is interesting to note: 1) 7/11 series find Class IV (diffuse proliferative) as the most common lesion while two find IIb (mesangial) and two find III (focal proliferative) to be most common. Normal light microscopy, Class I and IIa, and membranous, Class V, were never found to be most common. 2) The experience at Parkland is very close to the mean of the remaining ten series.

TABLE VIII

NO CLINICAL EVIDENCE FOR RENAL DISEASE BUT ABNORMAL BIOPSY

Series	Histologic Class	(n)	Normal Complement And Anti-DNA	Comment
Muehrcke (1967)	III	(1)	Not Done	
	V	(2)	Not Done	
Bardana (1975)	III	(9)	0/9	
Hollcraft (1976)	IIb III	(9)	6/9	8 patients rebiopsied without clinical or histologic change
Cavallo (1977)	IIb	(8)	Not Done	On rebiopsy 3 transformed to III, one with azotemia
Baldwin (1977)	IIb IV	(3) (1)	Not Done	
Mahajan (1978)	IIb	(3)	0/3	
	III	(12)	1/12	3 transformed to IV with azotemia
	IV	(12)	3/12	1 died uremic after 4 years
Appel (1978)	IIa IIb	(3) (4)	1/3	1 died of uremia after 4 years
Eiser (1979)	IIb III IV	(7) (3) (3)	4/13	
Woolf (1979)	III	(5)	0/5	None with renal dysfunction at 4-100 mo. followup
	IV	(1)	0	

TABLE IX

FREQUENCY OF HISTOLOGIC CLASS ON BIOPSY

Series		Number Of Biopsies	Histologic Class (% of biopsies) I or IIa	IIb	III	IV	V
Ginzler	(1974)	69		13	32	35	20
Mery	(1974)	69			46	54	
Zimmerman	(1975)	46	7	15	22	50	7
Kincaid-Smith	(1975)	54		55	6	30	9
Baldwin	(1977)	88		14	14	50	27
Lee	(1977)	50	14	24	30	12	20
Appel	(1978)	56	11	29	27	16	18
Mahajan	(1978)	90		4	36	52	8
Hill	(1978)	77	11	17	8	44	14
Cameron	(1979)	71		28	37	21	14
Parkland	(1980)	73		23	22	45	10
Total Biopsies		743	Mean %	4	20	25	37	13

IMPORTANCE OF THE AMOUNT AND LOCATION OF DEPOSITS

Comerford and Cohen (38) were the first to vigorously attempt correlation of the clinical picture, light microscopic findings, and electron microscopic findings in patients with lupus. They divided 13 patients with definite SLE into two clinical groups characterized in Table X. All patients had renal biopsies which were categorized by both light and electron microscopy. Light microscopic changes were graded quantitatively on the basis of glomerular and tubular changes taking into account hypercellularity, crescents, necrosis, wire loops, fibrinoid, leukocytic infiltration and capillary wall thickening on a scale of 0-3+. Electron microscopic changes were classified on the basis of location and number of electron-

TABLE X

CLINICAL CLASSIFICATION Comerford and Cohen (1967)

I. Minimal Or No Definite Clinical Renal Disease

   a. 24 hr protein <0.5 g or no more than 1+ protein on urinalysis
   b. Normal urine sediment
   c. BUN <20 mg% or creatinine <1.2 mg%

II. Definite Clinical Renal Disease

   a. 24 hr protein >1 gm
   b. Significant hematuria or cylinduria
   c. BUN >20 mg% or creatinine >1.2 mg%

TABLE XI

ELECTRON MICROSCOPIC CLASSIFICATION - Comerford and Cohen (1967)

I. No dense deposits in relation to the glomerular peripheral capillary wall.

II. Subepithelial or intramembranous dense deposits adjacent to or within the glomerular peripheral capillary walls. No subendothelial deposits.

III. Dense deposits in an immediately subendothelial location adjacent to the glomerular peripheral capillary wall.

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dense deposits as depicted in Table XI. Shown in a reproduction of the authors' Table 6 is the relationship between clinical, light microscopic, and electron microscopic classification. Two conclusions are apparent from this data. First, as previously discussed, there is a good correlation between clinical renal status and light microscopic findings. Second, both clinical status and the extent of abnormality on light microscopy correlate with electron microscopic changes. Clearly subendothelial deposits are associated with a worse clinical picture and more extensive histologic changes.

TABLE 6*

Correlation of Clinical, Light Microscopic and Ultrastructural Findings

Clinical Classification	Case	Degree of Involvement by Light Microscopy†	Electron Microscopic Classification*
No definite clinical renal disease	1	1+	Group I
	2	1+	Group I
	3	1+	Group I
	4	1+	Group I
	5	2+	Group I
	6	2+	Group II
	7 (ii)	2+	Group II
Definite clinical renal disease	7 (i)	3+	Group II
	8	2+	Group II
	9	3+	Group II
	10	3+	Group III
	11	3+	Group III
	12	3+	Group III
	13	3+	Group III

* See text for description of groups.
† 1+ slight, 2+ moderate, 3+ marked.

Although Comerford and Cohen set the stage, four subsequent studies (39-42) have confirmed their results and served to permanently entrench the concept that subendothelial deposits portend a poor prognosis. Grishman et al (39) studied 31 patients with SLE who had renal biopsies and were followed for up to 14 years. As illustrated in the authors' Table 4, the site of electron dense deposits correlated not only with clinical presentation, but also with ultimate renal outcome. Subendothelial deposits were again highly correlated with clinical evidence of significant renal disease and with one exception, predicted renal failure. Dujovne and colleagues (40) evaluated biopsy material from 24 patients, 12 of whom had repeat biopsies. Renal damage assessed by light microscopy was graded on a scale of 0 to 4+. Electron dense deposits were graded semiquantitatively on a scale of 0 to 4+. In addition the location of the deposits was classified as subendothelial, intramembranous, subepithelial and mesangial. These authors found that histologic activity did not correlate with the

extent of subepithelial or intramembranous deposits. While subendothelial deposits did correlate with activity, there were several exceptions. However, of note is that all patients who died with severe glomerulonephritis had 4+ subendothelial deposits in biopsies taken within weeks of death.

Table IV. Site of EM deposits in relation to clinical manifestations

Site of EM deposits	Number of cases	Renal disease				Outcome: renal failure
		none	mild proteinuria	severe proteinuria	nephrotic syndrome	
None	10	3	5	1	1	0
Mesangial	6	2	3	1	0	1
Subepithelial and mesangial	7	0	0	4	3	4
Subendothelial and subepithelial and mesangial	8	0	1	5	2	7

In the most recent study addressing this issue (41), renal biopsies from 13 patients were examined by light and electron microscopy and immunofluorescence. The authors' Table 2 correlates the light microscopic classification with the location and amount of electron dense deposits. Note that 6/7 patients with 3+ subendothelial deposits had diffuse proliferative glomerulonephritis (WHO Class IV) and 7/8 patients with nephrotic range proteinuria had 3+ subendothelial deposits. In addition, 4/7 with 3+ subendothelial deposits had a decreased creatinine clearance or azotemia.

Table 2. Sites and Extents of Electron-dense Deposits, Histologic Patterns of Lupus Nephritis, and Correlation with Proteinuria

	Light Microscopy	Ultrastructural Distribution			Proteinuria (g/24 hr)
		Subendothelial Deposits	Subepithelial Deposits	Mesangial Deposits	
Patient 1	Diffuse proliferative lupus nephritis	3	2	1	8.5
Patient 2	Diffuse proliferative lupus nephritis	3	2	1	18
Patient 3	Diffuse proliferative lupus nephritis	3	2	2 (E*)	6
Patient 4	Membranous lupus nephritis	3	3	2 (E)	3
Patient 5	Diffuse proliferative lupus nephritis	3	3	2	5.7
Patient 6	Diffuse proliferative lupus nephritis	3	2	2	7
Patient 7	Diffuse proliferative lupus nephritis	3	1	1	14.7
Patient 8	Membranoproliferative glomerulonephritis	2	3	2 (E)	20
Patient 9	Mesangial lupus nephritis	2	1	0	±
Patient 10	Mesangial lupus nephritis	2	0	2	0.5
Patient 11	Mesangial lupus nephritis	1	0	2	0
Patient 12	Mesangial lupus nephritis	0–1	0	0	0.8
Patient 13	Membranous lupus nephritis	1	3	1	±

* E = extraglomerular deposits.

Finally, in a more recent study (42) the evolution of subendothelial deposits assessed by repeat renal biopsy was correlated with clinical outcome, response to therapy, and light microscopic transformation in a group of 31 patients followed for a mean of 40 months (6-76 month range). In this study patients were selected for evaluation only if they exhibited subendothelial deposits in their first biopsy. They were then divided into three groups (all groups received similar therapy consisting of prednisone and a cytotoxic agent, usually azothiaprine) on the basis of their clinical outcome. Clinical criterea for follow-up evaluation are presented in Table XII.

TABLE XII

FOLLOW-UP CLINICAL EVALUATION - Hecht et al. (1976)

Improved	Urine protein excretion < 0.2 gm/24 hr
	and
	Normal renal function - creatinine < 1.5 mg%
Stable	Normal renal function - creatinine < 1.5 mg%
	and
	Urine protein excretion < 3.0 gm but > 0.2 gm/24 hr
Deteriorated	Serum creatinine > 1.5 mg%
	and/or
	Urine protein excretion > 3.0 gm/24 hr

As shown in the author's Table 2, the histopathological features on initial biopsy were similar by light microscopy and electron microscopy in all three outcome groups. Of major importance is the fact that the numbers and locations of deposits on EM were the same in the three groups--specifically subendothelial deposits. Table XIII shows the electron microscopic evolution and light microscopic transformation in these groups of patients. In the group of 20 patients with improved or stable function 17 were rebiopsied. Five lost all deposits, 11 lost all subendothelial deposits and one remained unchanged.

TABLE 2

Histopathological Features On Initial Renal Biopsy

Group	No. Bx.	Light Microscopy†			Electron Microscopy*		
		Mild	Moderate	Severe	Sub-end.	Mes.	Sub-epith.
Improved	12	3	2	7	2.7	2.8	1.0
Stable	8	2	2	4	3.0	3.1	1.6
Deteriorated	11	5	1	5	3.0	2.6	1.4

† Grading is based upon the distribution of pathological changes among glomeruli. Value provided is number of patients.

* Grading of deposits by electron microscopy is based on an index of 0 to 4.

Value provided is arithmetic mean.

TABLE XIII

EVOLUTION OF ELECTRON DENSE DEPOSITS - Hecht et al. 1976

	Number Rebiopsied	Complete Disappearance Of Subendothelial Deposits	Transformation To WHO Class V
Improved And Stable	17/20	16/17	11/17
Deteriorated	8/11	0/8	0/8

Interestingly 11 of the 17 transformed to a light microscopic picture most suggestive of membranous glomerulonephritis (WHO Class V). In the group that deteriorated 8 of 11 were rebiopsied. None showed loss of subendothelial deposits or transformation to a membranous picture (all had WHO Class IV or diffuse proliferative glomerulonephritis).

Therefore, taken in concert the above described studies would suggest the following: 1) Clinical renal status at biopsy usually correlates with light microscopic changes. 2) Both the degree of renal functional abnormalities and the severity of the light microscopic changes correlate with the presence of subendothelial deposits as found by electron microscopy. 3) Response to therapy or spontaneous improvement

in the renal lesion is correlated with the disappearance of subendothelial deposits. Presumably transformation of the light microscopic changes is a result of a change in the location of EM deposits.

TRANSFORMATION

Baldwin and colleagues (25) originally stressed that no matter what the histologic picture on original biopsy, patients did not switch from one category to another. However, their more recent experience and the experience of others do not support this notion. To be sure, our knowledge of the immunopathophysiologic basis for the various histologic classes and the mechanisms behind transformation from one class to another are incomplete. Discussion of this topic will be reserved for a subsequent Grand Rounds. However, while we are waiting for an answer to the immunologic basis for transformation, we should keep in mind the fact that clinical outcome is rather well correlated with histologic class. As a result, transformation from a "benign" to a severe histologic class or the reverse has clinical significance. Herein lies the importance of reviewing the incidence of changes in histologic class.

Pirani and Silva (43) have recently reviewed seven major studies of lupus renal disease in which a significant number of repeat biopsies were performed. In their Tables 1 and 2 are listed the incidence and types of histologic transformation. Although no attempt is made to explain the reasons for these transformations, three significant conclusions can be made from this data. First, since not all patients were rebiopsied the rate of transformation (32%) is a minimal estimate (even though repeat biopsies were more apt to be performed on patients whose clinical status had changed). Second, the most common transformation in the direction of a prognostically poorer class is from Classes II and III (mesangial and focal proliferative) to Class IV (diffuse proliferative)--28/34 that worsened changed from II or III to IV. Third, the most common "improvement" is from Class IV to Class V (membranous). It is thus apparent that the old notion of patients' renal disease remaining in one histologic class is not valid.

TABLE 1. INCIDENCE OF TRANSFORMATIONS IN LUPUS NEPHRITIS

Author	Total No. Points	No. Repeat Biopsy	No. Transformed	No. Not Transformed
Ginzler *et al.*[29]	69	31	9 (29%)	22
Hayslett *et al.*[32]	16	16	7 (44%)	9
Zimmerman *et al.*[60]	17	17	6 (35%)	11
Morel-Maroger *et al.*[46]	81	62	5 (10%)	57
Baldwin *et al.*[14]	88	31	16 (52%)	15
Cavallo *et al.*[20]	18	3	3 (100%)	0
Appel *et al.*[12]	56	22	11 (50%)	11
Total	345	182	57 (32%)	125 (68%)

TABLE 2. TYPE OF TRANSFORMATIONS IN LUPUS NEPHRITIS[a]

Initial Biopsy	No. Repeat Biopsies	No. Transformed	Class II	Class III	Class IV	Class V
Class II	60	17		4	11	2
Class III	43	20	1		17	2
Class IV	62	10	1	0		9
Class V	17	10	0	2	8	
Total	182	57	2	6	36	13

[a] Based on series by Ginzler *et al.*[29] Hayslett *et al.*[32] Zimmerman *et al.*[60] Morel-Maroger *et al.*[46] Baldwin *et al.*[14] Cavallo *et al.*[20] and Appel *et al.*[11]

TREATMENT

One of the most controversial aspects of renal lupus is therapy. Does treatment alter the natural course of renal disease? If so what treatment is preferred, taking into account the risk to benefit ratio? Who should be treated? With the understanding that certain histologic and electron microscopic patterns are associated with clinically significant renal disease and the possibility of transformation to a more severe lesion, does therapy directed at early lesions prevent clinical deterioration or transformation? Just as with other controversial therapeutic decisions, if the answers to these questions were readily available there would be no controversy. There have been numerous uncontrolled and controlled studies of therapy in lupus nephritis. At first glance one might think that every therapeutic alternative has roughly equal proof for and against its use. However, further analysis suggests that there is better evidence for certain therapeutic approaches.

STEROIDS

Since most rheumatologists and nephrologists who treat patients with lupus renal disease currently feel it is unethical to withhold steroid therapy, it is appropriate to begin by analyzing the evidence for the therapeutic efficacy of steroids in the renal disease of lupus.

Since renal disease in lupus is generally considered to be a result of immune complex deposition[1] in the kidney and the

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[1]There has been some recent work by Izui and collaborators (43-45) suggesting that glomerular basement membrane demonstrates an affinity for DNA. This finding coupled with their inability to demonstrate circulating DNA-anti-DNA antibodies in all patients (or experimental animals) with lupus has led to the postulate that immune complexes may be present in the glomerulus as a result of *in situ* formation.

resultant response of the kidney to the presence of these complexes (complement activation, cellular infiltration, activation of the coagulation system, mesangial, epithelial, and endothelial cell proliferation) there are several theoretic therapeutic rationale for the use of steroids. Steroids may be effective because of their anti-inflammatory effect, because they may affect glomerular capillary wall permeability, or because they have more specific affects on the immune system. High doses of steroids have been shown to decrease serum IgG in man by producing both increased catabolism and decreased synthesis (46). Steroid therapy (60 mg prednisone) has also been shown to produce significant decreases in circulating T and B lymphocytes in man (47). Finally, in a recent abstract (48) standard steroid therapy in patients with SLE nephritis has been shown to rapidly and predictably decrease circulating immune complexes.

The first group to evaluate the effects of large doses of prednisone on lupus renal disease was Pollak and his co-workers (49). This was not a controlled, prospective, or blinded study. They studied two consecutive but chronologically closely spaced groups of patients with biopsy proven renal lupus. The group of patients followed from 1953 to 1955 was treated in the convention for those days--low dose steroids (the equivalent of 10 mg prednisone). The group of patients followed from 1956 to 1958 was treated with high dose steroid (mean of 47.5 mg/day) for 6 months and then tapered to control systemic manifestations. The pertinent data are shown in Table XIV. It must be remembered that all patients had lupus glomerulonephritis (WHO Class IV). The conclusion that high dose prednisone was effective in this subset of patients is convincing. Further support for this conclusion comes from examining the effects of steroid dose on serial renal histology. In 25 serial biopsies on eight patients in the low dose group, glomerular damage worsened and lesions indicative of continued activity persisted in 7/8. In contrast, 37 serial biopsies on 14 patients in the high dose group showed decreased glomerular damage and loss of lesions of activity in all but four. It is important to note that no subsequent study evaluating any kind of therapy has had such complete histologic evaluation. Complications of high dose prednisone were frequent but non-fatal. Cushingoid habitus developed in 15/16, diabetes in five, non-fatal infections in four, osteoporosis in two, muscular weakness in two, and perforated peptic ulcer in one.

TABLE XIV

HIGH VERSUS LOW DOSE STEROIDS - Pollak et al. (1961)

	High	Low
Number	16	10
Glomerular Histologic Damage	2.75	2.70
Glomerular Histologic Activity	2.50	2.20
Duration Of SLE (Yrs)	2.1 (0.5-9)	2.1 (0.4-15)
Duration Of Renal Disease	11 (0-41)	10 (2-24)
Serum Creatinine mg%	1.55 (0.9-4.9)	2.00 (0.8-3.9)
Urea Clearance (% Normal)	38 (17-68)	32 (11-61)
Survivors (6/60)	9/16	0/10
Mean Follow-up To Death (Mo.)	13.4	13.8
Mean Follow-up Of Survivors	34.2	----

This report by The University of Illinois group was followed by two additional reports suggesting a benefit of high dose steroids on renal lupus (50, 51). Both studies included small numbers of patients (5 and 4) and one of them (50) included patients who recevied nitrogen mustard in addition. Thus they cannot provide support for the effectiveness of high dose steroids.

In 1964 Pollak and co-workers (52) extended their earlier work by reporting on 87 patients with SLE followed seven months to eight years (including the 26 patients reported on in their earlier study). Again, the results of therapy with high and low dose steroids were examined only in Class IV patients. Only 15 of the 47 patients with Class IV biopsies were alive at the end of the study after an average of 34 months post initial biopsy. Only one of these survivors was in the low dose group

(1/16) while 14 were in the high dose group (14/17). The percentage of patients in each treatment group dead due to renal failure is shown in the authors' Figure 5.

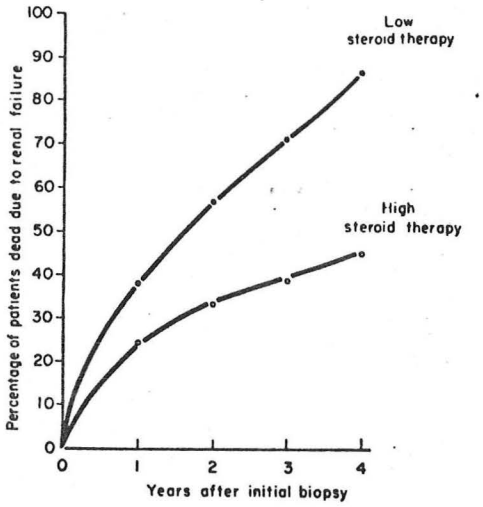

Fig. 5. Percentage of patients having active lupus glomerulonephritis and dying of renal failure in the first 4 years after the initial histologic study.

In a subsequent study on 14 biopsied patients (53) a convincing beneficial effect of high dose steroids was observed in spite of the fact that there was no low dose group for comparison and exact histologic class cannot be pinpointed for each patient. However, if just those patients with azotemia or decreased urea clearance are examined (ten patients) both BUN and urea clearance returned to normal in all but one on 60-100 mg prednisone daily for at least two months. Mean follow-up was 27 months and no patients died of uremia. Again, complications were frequent--all patients became cushingoid, three activated TB and three became psychotic.

In a recent publication, although the specific role of high dose steroids on renal lupus was not addressed, evaluation of the effects of steroids on survival in SLE (54) clearly showed greater survival in the modern high dose steroid era (209 patients treated between 1957 and 1968 compared to 156 patients treated from 1968 to 1975). Finally in a review addressed at the general question of steroids and survival in SLE, significant benefit was obtained in a "high risk" group which was not well described. Because pertinent details (number of patients with renal disease, type and extent of

renal disease, and amount of therapy) were not included in this review, its overall negative attitude to the therapeutic benefits of steroid must be viewed with caution.

AZATHIOPRINE

Largely because of the frequency of side effects with high dose steroid treatment but also in hopes of increased therapeutic response (based partly on the results in mice with SLE) physicians have turned to cytotoxic agents to treat renal involvement in SLE. Three relatively recent reviews (56-58) have summarized the uncontrolled and controlled clinical trials of cytotoxic agents in lupus renal disease.

Azathioprine is a purine analogue and owes its cytotoxic mechanism of action to its incorporation into DNA and interference with nucleic acid synthesis. In Table XV are listed the data from ten studies, both controlled and uncontrolled. It should be stated that in every study but one (63) at least low dose steroids were used in addition to azathioprine. In addition, in those studies that were controlled, azathiaprine was given for some time with high dose steroids except for two studies (63, 64). In these latter two studies azathioprine alone (63) or with minimal prednisone (64) was compared to the control groups. The results of the clinical studies outlined in Table XV can be summarized. First, from the uncontrolled studies, azathioprine does not add a clearcut beneficial affect when given with high dose prednisone. Second, from the controlled studies, half support (61, 63) and half refute (65, 67) a significant benefit from the use of azathioprine while one study (64) cannot be interpreted because of the short duration of treatment. It is fair to say that the efficacy of azathioprine as a sole agent or in addition to high dose steroids remains to be proven. However, one may consider using this agent in a patient who needs to have steroids tapered because of toxicity.

CYTOXAN

Cyclophosphamide (cytoxan) is an alkylating type cytotoxic agent that owes its mechanism of action to its chemical reactivity with nucleophilic centers of molecules such as DNA and RNA. Its use in the murine model (NZB/NZW F_1) of lupus has shown considerable benefit (68-73). Just as with azathioprine, cytoxan has undergone similar controlled and uncontrolled clinical trials. A summary of those studies is listed in Table XVI. It should be noted that only one study (76) compared cytoxan alone with the control group and only for a short duration of cytoxan therapy. The reason for this short duration was that all the patients were judged to be cytoxan treatment failures and switched to prednisone. In all other studies variable duration high dose prednisone and subsequent tapering

TABLE XV

AZATHIOPRINE (A) IN THE TREATMENT OF LUPUS NEPHRITIS

Series Ref.			Type (C/U)	# Pts. A	# Pts. C	Prior Steroids (A)	Control Rx	Duration A
Drinkard	(1970)	59	U	20	--	19/20	----	Throughout
Maher	(1970)	60	U	11	--	10/11	----	Throughout
Szteynbok	(1971)	61	C	16	19	16/16	Steroids	Throughout
Shelp	(1971)	62	U	12	--	10/12	----	Throughout
Cade	(1973)	63	C	13	15	NA*	Steroids	Throughout
Cade	(1973)	63	C	13	13	NA	A + Steroids	Throughout
Cade	(1973)	63	C	13	13	NA	A + Heparin	Throughout
Steinberg	(1974)	64	C	13	15	13/13	Steroids (low dose)	Ten Wks.
Hahn	(1975)	65	C	11	13	2/11	Steroids	Throughout
Hecht	(1976)	42	U	31	--	21/31	----	Throughout
Barnett	(1978)	66	U	47	--	46/47	----	Throughout
Sabbour	(1979)	67	C	11	67	7/11	Steroids	Throughout

*NA means either not available or not applicable.

TABLE XV (Cont.)

AZATHIOPRINE (A) IN THE TREATMENT OF LUPUS NEPHRITIS

Series Ref.		Histology III+IV+V		Decreased GFR		Nephrotic		Improved		Renal Deaths		Non Renal Deaths		Deaths Rx	
		A	C	A	C	A	C	A	C	A	C	A	C	A	C
Drinkard	(1970) 59	20	--	12	--	15	--	12	--	2	--	3	--	3	--
Maher	(1970) 60	11	--	5	--	5	--	3	--	1	--	3	--	0	--
Szteynbok	(1971) 61	NA*	NA	9	9	2	1	11	7	0	3	0	3	0	2
Shelp	(1971) 62	12	--	8	--	6	--	8	--	0	--	0	--	0	--
Cade	(1973) 63	13	15	13	15	8	8	10	3	4	7	0	2	0	2
Cade	(1973) 63	13	13	13	9	8	5	10	10	4	2	0	4	0	3
Cade	(1973) 63	13	13	13	13	8	10	12	9	4	2	0	2	0	1
Steinberg	(1974) 64	13	15	6	8	6	5	5	3	--	--	--	--	--	--
Hahn	(1975) 65	11	13	5	9	NA	NA	4	4	0	0	3	3	--	1
Hecht	(1976) 42	31	--	12	--	13	--	12	--	0	--	4	--	0	--
Barnett	(1978) 66	47	--	23	--	37	--	35	--	2	--	6	--	5	--
Sabbour	(1979) 67	11	67	BUN 37	BUN 39	NA	NA	NA	NA	5/11	43/67	5/11	16/67	NA	NA

*NA means either not available or not applicable.

TABLE XVI

CYTOXAN (CY) TREATMENT IN LUPUS RENAL DISEASE

Series Ref.			Type (C/U)	# Pts.		Prior Steroids (CY)	Control Rx	Duration CY
				Cy	C			
Cameron	(1970)	74	U	6	--	6	----	Throughout
Steinberg	(1971)	75	C	7	6	7	Steroids Low Dose	10 Wks
Fries	(1973)	76	C	5	5	NA*	Steroids High Dose	3-16 Wks
Feng	(1973)	77	U	31	--	31	----	Throughout
Steinberg	(1974)	64	C	10	15	10	Steroids Low Dose	10 Wks
Donadio	(1976)	78	C	19	20	19	Steroids High Dose	6 Mo
Donadio	(1978)	79	C	24	26	24	Steroids High Dose	6 Mo
Subbour	(1976)	67	C	32	67	17	Steroids High Dose	Throughout

*NA means either not available or not applicable.

TABLE XVI (Cont.)

CYTOXAN (CY) TREATMENT IN LUPUS RENAL DISEASE

Series Ref.	Histology III+IV+V		Decreased GFR		Nephrotic		Improved		Renal Deaths		Non Renal Deaths		Deaths Rx	
	Cy	C	Cy	C	Cy	C	Cy	C	Cy	C	Cy	C	Cy	C
Cameron (1970) 74	6	--	5	--	6	--	4	--	1	--	0	--	0	--
Steinberg (1971) 75	7	3	5	6	5	2	3	3	--	--	--	--	--	--
Fries (1973) 76	5	5	NA*	NA	1	1	0	4	0	0	1	1	1	1
Feng (1973) 77	28	--	4	--	6	--	28	--	2	--	5	--	1	--
Steinberg (1974) 64	10	15	7	8	2	5	4	3	--	--	--	--	--	--
Donadio (1976) 78	19	20	>10	>10	NA	NA	16	16	1	1	3	3	1	3
Donadio (1978) 79	24	26	17	20	NA	NA	21	21	1	1	3	4	2	4
Subbour (1976) 67	32	67	BUN 39	BUN 39	NA	NA	NA	NA	15	43	10	16	NA	NA

*NA means either not available or not applicable.

was administered along with cytoxan. Also of note is that the two studies by Donadio (78, 79) include 39 of the same patients in each study.

Except for the last study by Sabbour and Osman (67), which showed a significantly better survival in the cytoxan plus prednisone group, there is no evidence that improvement of renal function or survival is enhanced by the addition of cytoxan to prednisone and minor evidence that cytoxan alone is ineffective. However, it should be noted that Donadio (79) has found a significantly greater frequency of renal "flare-ups" requiring drug dosage changes in the prednisone group. If it can be shown that a patient with more "flare-ups" has a more rapid amputation of nephrons, there may be some evidence for a beneficial affect of cytoxan added to prednisone.

CHLORAMBUCIL

Chlorambucil is an alkylating agent like cyclophosphamide. Its use in the treatment of lupus renal disease has been more limited than either cyclophosphamide or azathioprine but generates more optimism.

There have been three major clinical trials of chlorambucil. The first is a small uncontrolled study (80) where six patients were treated with this agent. Five of the six were begun on chlorambucil because of progressive renal disease uncontrolled by toxic doses of corticosteroids. Important details of the study are outlined in Table XVII.

TABLE XVII

CHLORAMBUCIL TREATMENT OF LUPUS NEPHRITIS - Snaith (1973)

Patient Population	6 females mean age 32	
Biopsy	5/6 Class III + IV	
Duration Rx	3.25 Yrs.	
Renal Function	Before Rx	After Rx
24 hr urine protein - gm	6.8 (1-15)	0.9 (0-3.1)
creatinine clearance ml/min	54 (9-93)	85 (43-109)

The second study (81) claims to be uncontrolled. However, it includes 31 patients with Class IV renal lesions on biopsy who were all treated with high dose prednisone. After six weeks of prednisone treatment the patients were evaluated for steroid side effects, continued hypocomplimentemia, continued elevated anti-double stranded DNA, and continued urinary excretion of IgG L-chains. Sixteen patients exhibited at least one of these abnormalities and were begun on chlorambucil in addition to prednisone. It is interesting that no other abnormality of renal function was listed as an indication for chlorambucil. At any rate, if these authors were correct in their choice of parameters suggesting a non-optimal response to prednisone, their study then becomes one comparing incomplete prednisone responders to prednisone responders. If their choice of parameters were not good indices of beneficial steroid effect, then they indeed have a control group in their own population of patients. Table XVIII depicts their data rearranged into two treatment groups. Although the combined treatment group had a marked decrease in proteinuria compared to prednisone alone, the prednisone group did very well as a whole without a significant decrease in creatinine clearance or significantly more deaths. In view of this, it is difficult to evaluate the contribution chlorambucil made to the entire group survival.

TABLE XVIII

CHLORAMBUCIL TREATMENT IN LUPUS NEPHRITIS - Epstein (1974)

Treatment	Prednisone		Chlorambucil + Prednisone	
# Patients	15		16	
Duration SLE (mo)	51		60	
Duration Rx (mo)	40		16 (C only)	
Steroid Rx mg/day	30		22	
24 Hr Urine Protein gm	Before 3.2	After 3.7	Before 4.2	After 1.3
Creatinine Clearance ml/min	72	69	81	88
Renal Function				
Improved	3		8	
Stable	6		4	
Worse	6		4	
Deaths	4		3	

The final chlorambucil study is a recent publication (67) of a controlled trial comparing prednisone, prednisone plus azathioprine, prednisone plus cyclophosphamide, and prednisone plus chlorambucil. There were 163 total patients with biopsy proven Class III or IV (probably 23 Class III and 140 Class IV) lupus nephritis. Prednisone alone was given to 67 patients at least 60 mg for six weeks. Prednisone plus azathioprine was given to 12 patients (azathiprine was not available in Egypt during most of the study). Prednisone plus cyclophosphamide was given to 32 patients. Prednisone plus chlorambucil was given to 53 patients. Although the specific data were not given, serum urea and creatinine clearance were not different for the four treatment groups. The authors' Table 4 lists the survival rates at one to four years. Chlorambucil plus prednisone was significantly better than all other treatments and cyclophosphamide plus prednisone was significantly better than prednisone or prednisone plus azathioprine. In their Table 5 the authors analyze the causes of death in each group.

In view of the limited published information on chlorambucil in renal lupus one must be cautious not to be overenthusiastic about this agent. However, it is clear that controlled studies with chlorambucil should be of high priority in the U.S.

TABLE 4. Survival rates of patients under different therapeutic regimes

Therapeutic regime	% Survival rate after			
	1 year	2 years	3 years	4 years
Corticosteroids only	81	51	36	27
Corticosteroids + azathioprine	81	64	52	31
Corticosteroids + cyclophosphamide	90	80	73	67
Corticosteroid + chlorambucil	100	100	96	96

TABLE 5. Analysis of causes of death of patients under different therapeutic regimes

Therapeutic regime	Renal death	Non-renal lupus death	Other deaths	Total
Corticosteroids only (67 patients)	43	9	7	59
Corticosteroids + azathioprine (11 patients)	5	2	3	10
Corticosteroids + cyclophosphamide (32 patients)	15	3	7	25
Corticosteroids + chlorambucil (53 patients)	0	1	0	1
Total	63	15	17	95

PRELIMINARY INVESTIGATIONAL THERAPY

There are two other as yet infrequently tried therapies for lupus nephritis that merit brief discussion.

First, methyl prednisolone "pulse" therapy patterned after treatment of renal transplant rejection has been occasionally tried in lupus nephritis. Cathcart and colleagues (82) treated seven patients with diffuse proliferative lupus glomerulonephritis and rapidly deteriorating renal function. Five of seven patients with serum creatinines between 2 and 8 mg% improved within three days and within one month had creatinines of 0.8 to 2.2. Correction of serologic abnormalities (reduced complement, increased anti-DNA binding, and reduced T lymphocytes) occurred. All patients were started on low dose prednisone two weeks after pulse therapy and all were alive 6 to 30 months later without any symptoms of SLE.

Very recently the results of pulse therapy in 28 SLE patients has been reported (83). Pulse therapy was instituted in 25 of these patients specifically for control of active renal disease. Treatment was either 1 gm or 15 mg/kg methyl prednisolone IV daily for three doses. Four patients had large sustained improvement in renal manifestations (details not given); four patients with mean creatinine 5.7 mg% progressed to hemodialysis; one patient died of fulminant unresponsive lupus. Follow up was only four months and by that time about 50% of the patients had significantly improved renal function.

To date, because of the uncontrolled nature of the data steroid pulse therapy should be reserved for investigational purposes or for patients with clear-cut unresponsiveness (with respect to the kidney) to conventional treatment.

The second investigational therapy for lupus nephritis is plasmapheresis. The underlying rationale for such therapy is in part based on the alterations produced in the immune system (84). A 4 liter plasma exchange removes up to 65% of the circulating IgG keeping levels below normal from 2-20 weeks (84). In addition C_3, C_5 and factor B are significantly reduced for up to 48 hours (84). Also, plasmapheresis may have an effect on reticuloendothelial function in that ^{51}Cr labeled IgG coated red cells are cleared more rapidly after plasmapheresis (84). Finally, circulating immune complexes have been shown to decrease with plasmapheresis (85). Whether these or other effects of plasma exchange are responsible for any of its potential benefits remains to be clarified. Published results of this therapy for lupus nephritis (84-86) include too few patients to justify any conclusion on its efficacy.

SEROLOGIC SURVEILLANCE

It is obvious that at initial presentation of patients with SLE, during follow-up on patients without previous evidence of renal disease, and during treatment of patients with known renal disease, urine sediment examination, quantitative urine protein excretion, and measurement of creatinine clearance should be done and will play a major role in decision making. However, are there measureable serologic parameters than can help predict the presence and/or type of renal involvement, predict renal "flare-ups", document adequacy of therapy, and warn the physician when therapy is being changed too quickly or inappropriately? Several serological parameters have been evaluated. These include various complement measurements, anti-DNA antibodies and circulating immune complexes.

Cameron and collaborators (87) reviewed sera from 32 patients with biopsy-proven lupus nephritis and correlated C_4 concentrations and DNA binding by the Farr technique with clinically assessed renal disease activity. From their Table 10 one can conclude that anti-DNA measured by the Farr technique is abnormal more often than C_4 measurements if there is renal involvement in SLE, but that C_4 is a better index of activity of renal disease. Since serial measurements and therapy data, as well as results in patients with SLE and no renal involvement, were not included in this study, one cannot determine whether diagnostic accuracy for presence or activity of renal disease could have been improved. Using the newly developed Crithidia luciliae test for anti-DNA antibody (88), this same group (89) found that this assay was more specific than the Farr assay with respect to lupus renal disease, but that its sensitivity was a bit less. In addition, the titer of positive Crithidia tests did not correlate with clinical judgements of disease activity.

Table 10 Relationship Between "Activity" of Renal Disease Serum C4 Concentrations and DNA Binding

	Numbers of Points Assessed		
	Active[a] Renal S.L.E.	Inactive[a] Renal S.L.E.	
C4 Concentration			
< 50%RNS[b]	60 (67%)	15 (24%)	
>50%RNS	30 (33%)	114 (76%)	
Totals	90 (100%)	150 (100%)	(240)
DNA Binding			
>20%	60 (89%)	103 (74%)	
<20%	7 (11%)	36 (26%)	
Totals	67 (100%)	139 (100%)	(206)

[a] Active = score of 3–7; inactive = score of 0–2 (see Table 9).
[b] Reference normal serum.

Subsequent studies have found more utility for the Crithidia test. Chubick and collaborators (90) from this institution measured antibody to native DNA by five different methods in patients with SLE, mixed connective tissue disease, other diseases and normals. With respect to sensitivity and specificity for SLE and SLE with severe nephritis, none of the other assays were significantly better and in several circumstances they were all worse. The Crithidia data is shown in Table XIX. Of note is that all but one patient with active SLE and a significant renal biopsy abnormality had a positive Crithidia test. In a subsequent study (91) the sensitivity and specificity of this test was confirmed and additional studies done serially on 24 patients with SLE, 14 of whom had active renal disease. Although details of treatment and individual patient response are not given, successful treatment in 18/19 of these patients was associated with a fall in titer. Of interest is that after initial successful treatment rises in titer occurred eight times. All eight instances were associated with clinical exacerbations. Of greatest interest, but apparently not yet available, would be serial anti-DNA titers by this method in patients with SLE who are biopsied and histologically classified in an attempt to correlate the presence and change in titer of anti-DNA with changes in clinical activity of renal disease monitored by proteinuria, sediment, and creatinine clearance. Although data using the Crithidia assay are not available to address this issue, an older study (92) examined serial anti-DNA binding capacity using the Farr technique in 21 patients with biopsy proven lupus glomerulonephritis on immunosuppressive therapy. Two patterns of serial anti-DNA binding capacities were found. One group showed a persistent high titer (pattern B) over the 24 month follow up (8 patients) while another group (13 patients) either started out with low titers or showed a decrease and then persistently maintained a low titer (pattern A). Table 20 shows the clinical characteristics of these groups. All patients with pattern B deteriorated clinically while only one with pattern A deteriorated.

In addition to attempts to correlate the presence and titer of anti-DNA antibodies with lupus renal disease and its activity, several studies have addressed the question of the nature of the anti-DNA antibody; i.e. immunoglobulin class, avidity for DNA, complement fixing ability, precipitating or non precipitating. Such an examination is a logical sequel to the realization that not all SLE patients with circulating anti-DNA antibodies develop renal disease.

With respect to the nature of the anti-DNA immunoglobulin, a recent study (92) from this institution of 27 patients with SLE--14 with nephritis and 13 without based on biopsy and clinical criteria--examined the immunoglobulin class, sub-class

TABLE XIV

CRITHIDIA LUCILIAE TEST FOR ANTI-DNA IN SLE - Chubick (1975)

	No. + / No. Tested	%
Sensitivity For SLE	32/56	57
Sensitivity For Severe Lupus Nephritis (IIB-V)	16/22	73
Active SLE	12/13	92
Inactive SLE	4/9	44
	No. + With Characteristic / Total No. +	%
Specificity For SLE	32/40	80
Specificity For Severe Lupus Nephritis	16/32	50
Active SLE	12/23	52
Inactive SLE	4/9	44

and complement fixing ability. As shown in their Table 2, titer of anti-native DNA was higher in patients with nephritis. Of significance was the fact that 13/14 patients with nephritis had high titer complement fixing anti-native DNA while only 4/13 patients without renal disease had complement fixing anti-native DNA antibodies and then only detectable in undiluted serum. In addition, as shown in their Table 3, IgG antibody subclasses G1 and G3 (the subclasses capable of complement fixation) were the only IgG subclasses present in serum of patients with nephritis and then more frequently than in patients without renal disease. Subsequently another group (94) has published evidence that disappearance of complement fixing anti-DNA as measured by Crithidia heralded remission of disease activity in six patients followed serially (four had biopsy proven active renal lupus--one Class III and three Class IV).

TABLE XX

PROGNOSTIC SIGNIFICANCE OF SERIAL ANTI-DNA's - Adler (1975)

	BUN		Creatinine		24 Hr Urine Protein (gm)	
	Initial	Final	Initial	Final	Initial	Final
Pattern A (low titer)	18.2	13.2	1.04	0.92	2.02	.68
13 Pts.	(10-36)	(7-26)	(0.4-1.4)	(0.6-1.5)	(0.1-5.9)	(0.1-3.6)
Pattern B (high titer)	32.5*	90.6	1.53	4.4	3.8	7.3
8 Pts.	(15-32)	(33-110)	(.7-1.7)	(1.4-8.9)	(0.4-9.5)	(2.2-11)
	108	241	3.8	5.9	9.5	11.0

*Means in pattern B include one patient very azotemic initially. Values for that patient are depicted below the range.

TABLE 2
COMPARISON OF SEROLOGICAL DATA IN SLE PATIENTS WITH AND WITHOUT NEPHRITIS

SLE patient group	Median anti-nDNA titer	Median CF-anti-nDNA titer	Low total serum hemolytic complement (number positive/ number tested)
With nephritis ($N = 14$)	1/1280 $P < 0.005$	1/80 $P < 0.001$	7/11 $P > 0.05$
Without nephritis ($N = 13$)	1/160	Neg.[a]	3/10

[a] Four patients did have CF-anti-nDNA detectable only when undiluted sera were assayed.

TABLE 3
IgG NATIVE DNA ANTIBODY SUBCLASSES IN SLE PATIENTS WITH AND WITHOUT NEPHRITIS

SLE patient group	Two-step IIF assay* with undiluted serum[a] (number positive/number tested)			
	G1	G2	G3	G4
With nephritis ($N = 14$)	11/14 $P < 0.01$	0/14	9/14 $P < 0.01$	0/14
Without nephritis ($N = 13$)	2/13	0/13	1/13	0/13

[a] *Crithidia luciliae* native DNA substrate plus patient serum followed by FITC-conjugated rabbit or monkey antisera to human IgG1–IgG4.

In addition to immunoglobulin class, subclass, and complement fixing ability, avidity for DNA has been examined (95). High avidity anti-DNA was found in glomerular eluates of lupus kidneys while low avidity antibody was found in serum during active glomerulonephritis. Interestingly, high anti-DNA antibody titers in patients with active SLE but without evidence of nephritis, was high avidity antibody.

Finally, another twist in the anti-DNA antibody story has recently been published (96). Utilizing circular DNA from the bacterophage PM_2 of pseudomonas in the Farr technique, these investigators followed 78 patients with SLE for two years measuring anti-DNA titer every six weeks. They found a sharp drop in anti double stranded DNA (usually proceeded by a rise) titer associated with clinical exacerbations. In addition only when anti-DNA titer measured with this technique was associated with low levels of $C1_q$ and C_3 was clinical renal involvement evident. These unique findings certainly need to be confirmed.

The most recent addition to the serological surveillance techniques is the measurement of circulating immune complexes. In four recent series (97-100) using several different techniques for measurement of circulating immune complexes, 72/85 (85) patients with SLE and definite renal disease had detect-

able serum levels. Thus this test already has approached the sensitivity of the anti-DNA assays. It is probable that further characterization of these complexes, just as with anti-DNA antibodies, will lead to even more sensitive and specific tests for active renal disease or response to treatment.

END-STAGE RENAL FAILURE IN SLE

Several investigators have noted an interesting phenomenon in SLE patients who have developed uremia from progressive lupus nephritis. The vast majority of these patients lose both the clinical and serologic manifestations of SLE. Fries and colleagues (101) reported on 13 patients who developed renal failure from SLE nephritis. A summary of these patients' clinical and serologic parameters is shown in Table 4 from this manuscript. Several points should be noted. First, disease activity estimated by clinical criteria was much reduced, with skin and joint activity (the hallmarks of active SLE in non-uremic patients) being virtually absent. Second, signs of serologic activity are reduced or absent. Third, hypertension is more frequent and more severe. Finally, all these changes occur despite marked reductions in steroid and immunosuppressive therapy. A more recent review (102) of 30 uremic patients with SLE substantiates this finding. Shown in Table XXI are the characteristics of this second group of patients.

Table 4. *Two Stages of Lupus Nephropathy: Mean Values*

	Early-Stage (Active) Lupus Nephritis	Late-Stage Lupus Nephropathy
Clinical (0-4+)		
Skin	1.7	0.2
Joints	2.0	0.0
Serositis	1.0	0.4
Systemic	3.2	2.2
Serologic		
LE Prep	+	—
FANA Titer	1:213	1:62
Anti-DNA/Titer	1:62	1:4
Complement(B_1C-mg%)	58	83
Functional		
Hematocrit (%)	27	20
Blood Pressure (mm Hg)	145/90	183/117
Creatinine (mg %)	1.6	10.5
Proteinuria (0-4+)	3.9	2.2
Therapy		
Prednisone (mg/dy)	65	17
Immunosuppressives	9/13	2/13

TABLE XXI

REGRESSION OF CLINICAL AND SEROLOGIC SLE IN UREMIA - Brown (1979)

	Pre-Azotemia	During Dialysis
Skin	24/30	4/30
Joints	29/30	4/30
Positive LE Prep	22/29	0/16
Positive ANA	21/24	6/24
Anti-DNA	6/8	5/15
Low C_3	23/26	2/22
Prednisone Rx	30/30	6/30

There are two major patient management implications of these changes. First, one must not overtreat these patients with steroids and immunosuppressives because their requirements are lower. Second, one must be even more careful than in the non-uremic patient with SLE not to ascribe certain clinical occurrences to SLE since the chances that various signs and symptoms are due to active lupus are much less.

Finally, how successful have maintenance hemodialysis and transplantation been in these patients? Table XXII lists the hemodialysis and transplant experience of several groups. Both the experience of the New York and Dallas groups has been favorable arguing for aggressive support of these patients.

With respect to transplantation, a recent report from the ASC/NIH Transplant Registry (103) lists 56 patients with SLE. Cadaver grafts were placed in 29 and 27 received grafts from living related donors. Overall patient survival after two years was 66% with graft survival being 55%. However, living related graft survival was 80% while cadaver graft survival was 32%. No patient developed documented recurrent lupus in the transplanted kidney. While these statistics are not as good as the experience in the general transplant population, they are not prohibitively grim. Indeed, a more recent report from a very active transplant center (104) reports on ten patients all alive after one year with graft survival of 80% (five cadaver grafts and three living related grafts). These authors also reported no evidence for recurrent lupus renal disease.

TABLE XXII

HEMODIALYSIS IN END STAGE LUPUS NEPHROPATHY

Series	Ref.	Entered Dialysis	Deaths On Dialysis	Duration Dialysis (Survivors)
Gral (1970)	101	5	4 (<16 mo.)	
Brown (1979)	102	30	5	
Dallas (1980)		23	8 (2-58 mo., mean 25 mo.)	31 mo. (4-90 mo.)

Finally, because of the recent favorable reports of dialysis and transplantation in end-stage renal disease, we need to be wary of the therapeutic risks involved in aggressive steroid and immunosuppressive drug administration in an attempt to salvage renal function.

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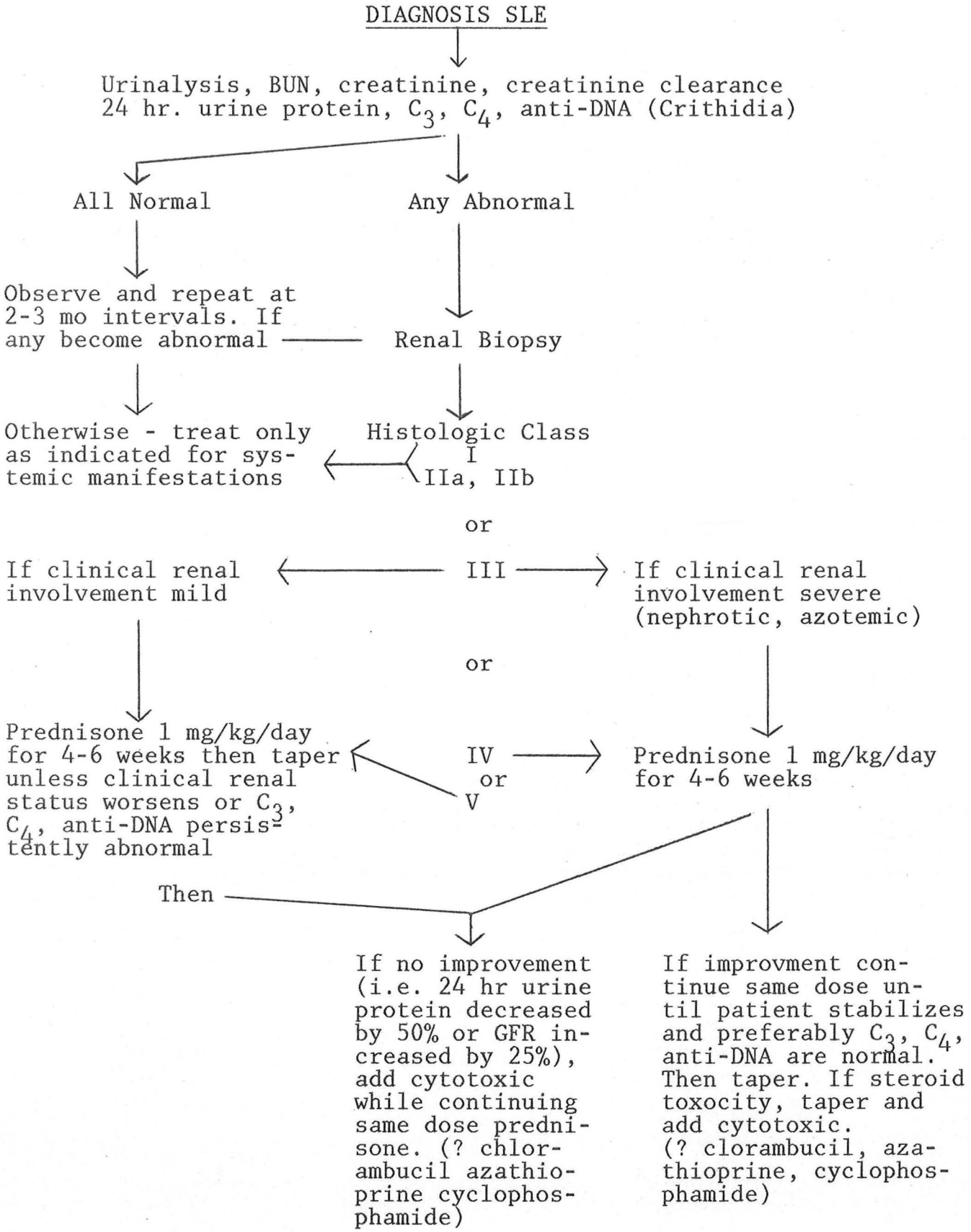
DIAGNOSIS SLE
Urinalysis, BUN, creatinine, creatinine clearance
24 hr. urine protein, C_3, C_4, anti-DNA (Crithidia)
All Normal
Any Abnormal
Observe and repeat at 2-3 mo intervals. If any become abnormal
Renal Biopsy
Otherwise - treat only as indicated for systemic manifestations
Histologic Class
I
IIa, IIb
or
III
If clinical renal involvement mild
If clinical renal involvement severe (nephrotic, azotemic)
or
Prednisone 1 mg/kg/day for 4-6 weeks then taper unless clinical renal status worsens or C_3, C_4, anti-DNA persistently abnormal
IV
or
V
Prednisone 1 mg/kg/day for 4-6 weeks
Then
If no improvement (i.e. 24 hr urine protein decreased by 50% or GFR increased by 25%), add cytotoxic while continuing same dose prednisone. (? chlorambucil azathioprine cyclophosphamide)
If improvment continue same dose until patient stabilizes and preferably C_3, C_4, anti-DNA are normal. Then taper. If steroid toxocity, taper and add cytotoxic. (? clorambucil, azathioprine, cyclophosphamide)