The natural history of the renal manifestations of systemic lupus erythematosus

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Serial clinical observations and histologic studies were made on the kidneys of 87 patients with systemic lupus erythematosus over periods ranging from 7 months to 8 years. A total of 176 renal biopsy and necropsy specimens were analyzed in detail by a semi-quantitative method, and the histologic findings were classified in the following four groups: normal kidney, lupus glomerulitis, active lupus glomerulonephritis, and membranous lupus glomerulonephritis. Forty patients in whom the initial findings were normal kidneys, lupus glomerulitis, and membranous lupus glomerulonephritis were followed for 160 patient-years. During this period only 2 developed mild lupus glomerulonephritis which responded to treatment, and 2 others developed severe disease and died in renal failure. Progression from the milder forms of renal involvement to severe active lupus glomerulonephritis was uncommon. Most patients with active lupus glomerulonephritis died in renal failure, but the clinical and histologic progression of the disease was slowed or halted in many by prolonged treatment with large doses of prednisone.

In 1922 Keith and Rowntree reported upon 4 patients with lupus erythematosus and nephritis and stressed that "nephritis was a common complication of disseminated lupus erythematosus." Nine years later Baehr pointed out the importance of renal complications in Libman-Sacks endocarditis in the first of a series of papers on systemic lupus erythematosus (SLE). Since that time, histologic abnormalities of the kidney have been reported in at least 75 per cent of patients with SLE on whom postmortem studies have been made, and renal failure is the commonest cause of death in patients with SLE.

The use of serial percutaneous renal biopsies in studying the clinical and histologic aspects of renal involvement

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in SLE has been described previously from this laboratory. Forty-one patients with SLE were followed for periods ranging from 2 months to 2 years. The kidneys of some patients were normal histologically; lupus glomerulitis and lupus glomerulonephritis were diagnosed in the kidney biopsies of others. It was inferred that lupus glomerulitis was the early stage of a lesion which progressed to lupus glomerulonephritis in many patients.

The present study is of 87 patients with SLE, including those previously described, in whom renal biopsies were made and who were followed over periods totaling 7 months to 8 years. Serial clinical observations and laboratory tests were made, and 176 histologic specimens were analyzed in detail.

As described previously, the kidneys in patients with SLE may be normal histologically, or lupus glomerulitis or lupus glomerulonephritis may be found. Active lupus glomerulonephritis, a rapidly progressive disease, has been described by many observers. When the accumulated renal tissue sections were analyzed, another histologic pattern—diffuse membranous glomerulonephritis—was recognized and separated from the others.

The previous inference that lupus glomerulitis was frequently the forerunner of lupus glomerulonephritis will be shown to be incorrect. Patients in whom the initial findings were normal kidneys or lupus glomerulitis did not, with few exceptions, subsequently develop lupus glomerulonephritis and did not die of progressive renal disease. Likewise, there was little clinical or histologic evidence of progression of the renal disease in patients with the membranous type of lupus glomerulonephritis. In contrast with these findings, most patients with active lupus glomerulonephritis died in renal failure unless they received large doses of prednisone for a long period.

**Material and methods**

*Selection of patients for study.* Systemic lupus erythematosus was diagnosed by the occurrence in combination of a variety of abnormal clinical findings and laboratory tests. The presence of LE cells was not regarded as *sine qua non* for the diagnosis of SLE, although LE cells and/or antinuclear antibodies were found in the serum of almost all patients. These diagnostic criteria for SLE were fulfilled in over 150 patients seen between 1958 and January 1962. Only patients satisfactorily meeting the criteria are included in this study. Those in whom the diagnosis was equivocal—e.g., possible rheumatoid arthritis, possible SLE—were excluded.

The incidence and significance of renal abnormalities in SLE were studied from 1958 to 1955. During this period, percutaneous renal biopsies were done whenever possible on all patients with SLE—whether or not there was clinical evidence of renal involvement. From 1956 on, renal biopsies were done on almost all patients with SLE in whom there were persistently abnormal urinary analyses and/or proteinuria and/or impairment of renal function. Biopsies were not made on most patients having no clinical or laboratory evidence of renal disease. In a few patients first seen shortly before death, biopsies were not made.

All renal biopsy and necropsy specimens from patients with SLE were filed together alphabetically, whatever the histologic diagnosis. Thus, they were available for detailed examination by an independent observer, who knew only that they were taken from patients with SLE and who had no knowledge of the clinical or laboratory data.

*Selection of histologic material for study.* As our main object was to describe the natural history and course of renal involvement in SLE, the 1940s and early 1950s. As knowledge developed and antibiotics and better supportive treatment became available, patients with SLE survived longer, renal disease seemed to be a frequent and prominent "complication," and renal failure a more common cause of death than hitherto perceived.

Bob Kark appreciated the contribution that liver biopsy was then making to the study of hepatic disease and thought that percutaneous renal biopsy might lead to a better understanding of diseases of the kidney. The new biopsy technique developed in Copenhagen was modified and improved in Chicago by Kark and Bob Muehrcke. The renal group of the University of Illinois College of Medicine developed when they were joined by Conrad Pirani and Victor Pollak.

When patients with SLE were admitted to the hospital, an understanding of the clinical and pathological renal manifestations of their illness was lacking. Blood and urine studies correlated very poorly with severity of the renal disease. One of the first patients in our studies typifies the understanding of medical renal diseases and of lupus nephritis in particular at that time. In the biopsy of a patient with SLE who had red cells and casts in the urine, one of us (Dr. Pirani) detected lesions in some glomeruli that he considered as typical of focal embolic glomerulonephritis. The patient, it seemed, had bacterial endocarditis, possibly superimposed on Libman-Sacks endocarditis. The clarity of this conclusion was shattered by six negative blood cultures. This lesion would be classified today as WHO Class III lupus nephritis. A short while later, several patients were referred with pyelonephritis, because there were abnormal numbers of white blood cells in the urine. The diagnosis was not sustained because urine cultures were repeatedly negative; glomerular lesions of mild degree (now WHO Class II) were found on biopsy.

These early experiences revealed the paucity of knowledge of the time and pointed to ways in which new light might shatter old beliefs. They highlighted the value of correlations between clinical findings, laboratory tests, and contemporaneous examination of the underlying structural abnormalities. They led to the decision to embark on an extensive study of the renal disease in patients with SLE.

Renal biopsy provided an opportunity to study lupus nephritis not only in its early stages but also, with sequential specimens, to obtain valuable information on the natural history of the disease, on the effect of therapy, and on the correlation of histopathologic findings with clinical and laboratory data obtained at the time of biopsy. During the course of these ten years, understanding of the histopathology advanced when histologic sections, originally thick (6 μm), became thin (2 μm), and when at that time the new disciplines of electron microscopy and immunopathology were applied systematically in interpretation of individual histopathologic lesions.

To achieve the goals of our studies, a new approach was needed. First, different lesions in the glomeruli, tubules, interstitium, and vessels needed to be more precisely defined. Second, the severity of these lesions had to be assessed and scored by two independent observers without...
following tissue sections were excluded from the study: (1) biopsies made within 3 to 4 days of death; (2) necropsy specimens, except when a previous renal biopsy was available; (3) specimens in which tissue was inadequate for semiquantitative analysis; (4) specimens obtained from patients seen only in consultation and returned to the care of their personal physicians at other hospitals.

When these exclusions had been made, 155 biopsy and 21 necropsy specimens were available for study on 87 patients with SLE. Analysis of these specimens forms the basis for this paper. The first biopsy on these 87 patients was made between January, 1952, and January, 1968. Follow-up data were obtained up to July 31, 1962.

Methods of histologic analysis of specimens of renal tissue. Renal biopsies taken according to the technique of Kark and Muehlecke,4 were fixed in 10 per cent neutral formalin from 1958 to 1958 and in Helly's solution from 1958 to 1962. Tissue specimens were cut at 5 to 6 μ early in the study; later sections were cut routinely at 2 to 3 μ. Old blocks were recut at 2 to 3 μ whenever possible. All sections were stained with hematoxylin and cosin, periodic acid-Schiff, or alcian blue and periodic acid-Schiff, and Masson or Mallory trichrome techniques; some were also stained with silver methenamine.

Table 1. Histologic findings considered to reflect the presence or absence of activity of the renal lesions in patients with SLE

<table>
<thead>
<tr>
<th>Glomeruli</th>
<th>Active lesions</th>
<th>Inactive lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local necrosis</td>
<td>Basement membrane thickening</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>Cellular proliferation</td>
<td></td>
<td>Adhesions</td>
</tr>
<tr>
<td>Karyorrhexis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinoid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wire loops</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematoxylin bodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyaline thrombi (rare)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitium</td>
<td>Infiltration by plasma cells and lymphocytes</td>
<td>Infiltration by lymphocytes</td>
</tr>
<tr>
<td>Arteries and arterioles</td>
<td>Fibrosis</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>Fibrinoid</td>
<td></td>
<td>Hyalination</td>
</tr>
</tbody>
</table>

Semi quantitative histologic analyses were made, and a scale from normal (0) to extremely severe (+++) was used. The method used has been described previously,4 and its reproducibility has been shown.8 The over-all damage to glomeruli, tubules, arteries, arterioles, and interstitial tissue was graded from 0 to ++. The grading of activity was based on an overall impression, rather than on a summation of the degree of involvement of each individual component. When the semiquantitative evaluation had been completed, one of the following four histologic diagnoses was made: normal, lupus glomerulitis, active lupus glomerulonephritis, or membranous lupus glomerulonephritis.4

Clinical and laboratory methods. The biochemical and immunologic methods have been described previously.4 Two-hour creatinine clearances were done; creatinine was analyzed by the method of Peters.6 The patients were treated in the hospital when necessary and were followed in a special outpatient clinic at appropriate intervals dictated by their clinical course. When indicated, renal biopsies were repeated to evaluate the evolution of the histologic changes. Urinalysis and tests of renal function were done on all occasions when renal biopsies were made and at appropriate periods throughout the course of follow-up.

The patients were treated by conventional methods with full supportive treatment when indicated and with sufficient cortisol or its analogues to control the clinical manifestations of the disease. Cortisol or cortisone was used until 1956; thereafter prednisone was given. Additional treatment was given as indicated for the nephrotic syndrome, for chronic renal failure, and for infection and other intercurrent illnesses. Certain patients received chloroquin for short periods of time, but no drugs other than corticosteroids were used. The patients were followed in the hospital and at follow-up visits to the outpatient clinic. The tests of renal function were designed to follow the course of the disease and the effects of therapy, to reconstruct the natural history of the disease, and to begin to estimate prognosis and the potential effects of therapy. It was the quantification of individual elements of the histology and their sequential study over time, combined with sequential clinical observations, that enabled division of the histopathologic changes into two groups: (1) active lesions characterized by proliferative, inflammatory, and necrotizing features that were considered to be fairly rapidly progressive but likely to respond to therapy and to be at least partially reversible; and (2) inactive lesions characterized by sclerosis, fibrosis, and atrophy that were only slowly progressive but unlikely to respond to therapy. Scoring of the severity of different active or acute and of inactive or chronic lesions led to the later development of the widely used indexes of activity and chronicity, and the World Health Organization (WHO) classification.

In the years between 1964 and 1997, advances have taken place in many fields that bear upon The Natural History of the Renal Manifestations of Systemic Lupus Erythematosus. First, using immunopathologic and ultrastructural methods, several "new" histopathologic lesions were identified, which were particularly related to the amount, type, composition, and position of immune complex deposits. Second, new therapeutic approaches have favorably influenced the natural history of the disease and illustrated the biological importance of the various types of histopathologic lesions.

Changes in the practice of medicine and in referral of patients appear to have greatly influenced the time of presentation of the patient to nephrologists and the characteristics of the lesions seen. In almost all published series from North America since 1971, there was a high proportion with significant glomerular sclerosis in an initial renal biopsy, suggesting that patients are first studied very late in the course of their disease. Perhaps it is not surprising that many patients with SLE develop end-stage renal failure.

Review of the details of our initial biopsies for the ten years, 1954 to 1964, revealed sclerosed glomeruli in a single initial biopsy. In 1964, we stressed the critical importance of early diagnosis and early and effective treatment. Our data showed the importance of meticulously conducted and interpreted urinalysis and simple tests of renal function in the early diagnosis. Two decades earlier, the great Stanford nephrologist Addis taught the value of urinalysis and predicted that the urinary findings would be shown to reflect the type of injury to the kidney. In an earlier publication on these patients with SLE, we demonstrated the wisdom of Addis. There were 60 renal biopsies from patients in whom a urinalysis was performed contemporaneously by the nephrologist on a freshly voided, concentrated early morning specimen of urine. An abnormal urinalysis (with more than a few red cells or white cells) predicted significant glomerulonephritis in the biopsy (χ² = 31.8, P > 0.001). This simple, inexpensive, and highly accurate predictive test is no longer in use. A urine specific gravity >1.024 after 14

* These terms will be defined fully in the Results.
tisone or prednisone were used systematically in the treatment of these cases. As indicated in the discussion of results, particular patients with lupus glomerulonephritis received large doses of prednisone for 6 months or longer, irrespective of their clinical symptoms. These patients were so treated from 1956 on.

Results

The patients were divided into four groups on the basis of the histologic findings in the initial renal biopsy (Table II).

Table II. Summary of histologic diagnoses and semiquantitative analysis of the findings in the first renal biopsy from 87 patients with SLE

<table>
<thead>
<tr>
<th>Histologic diagnosis in initial biopsy</th>
<th>No. of patients</th>
<th>Average score* of damage</th>
<th>Overall renal damage</th>
<th>Overall cellular activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal kidney</td>
<td>10</td>
<td>0.0 0.0 0.0 0.0 0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Lupus glomerulitis</td>
<td>23</td>
<td>0.7 0.8 0.2 0.1 0.0</td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Membranous lupus glomerulonephritis</td>
<td>7</td>
<td>1.1 0.9 0.6 0.4 0.2</td>
<td>1.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Active lupus glomerulonephritis</td>
<td>47</td>
<td>2.2 1.5 0.4 0.6 1.4</td>
<td>2.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Treated subsequently with low steroid dosage</td>
<td>10</td>
<td>1.9 1.5 0.5 0.8 1.6</td>
<td>2.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Treated subsequently with high steroid dosage</td>
<td>21</td>
<td>2.3 1.5 0.3 0.5 1.3</td>
<td>2.1</td>
<td>1.9</td>
</tr>
</tbody>
</table>

*Maximal score: 4.0 (see text).

1. There was no histologic evidence of renal involvement in 10 patients.
2. Lupus glomerulitis, a lesion characterized by mild local and focal changes in the glomerular tuft with no significant tubular or interstitial changes, was diagnosed in the initial renal biopsy of 28 patients. The lesion was characterized by small local areas of endothelial or axial hypercellularity, particularly at the periphery of the glomerular tufts. In association with these cellular changes there was a mild and irregular local and focal thickening of the capillary basement membrane. Evidence of activity in the lesions was found in only 2 instances.
3. Active lupus glomerulonephritis was diagnosed in the initial biopsy of 47 patients. In this condition the glomeruli were involved by a more severe proliferative and membranous process, frequently associated with necrotizing features, and there were definite tubular and interstitial changes. The lesions were usually pleomorphic, and a wide variety of individual abnormalities was seen in any single renal biopsy. Parts of each glomerulus were affected rather than whole glomeruli, and the lesions within the glomerulus were relatively local until a late stage. Many glomeruli were severely involved in some cases; severe involvement was focal in others. Local necrosis with obliteration of capillary loops, karyorrhexis, and fibrinoid changes usually affected some, but not all, of the glomeruli. These lesions occurred in association with areas of glomerular hypercellularity. Hematoxyphil bodies were found in some instances, hyaline thrombi more rarely, and on occasion a few polymorphonuclear leukocytes were seen in these areas. Reactive proliferation of visceral epithelial cells and later of the parietal cells of Bowman's

hours of dehydration (χ² = 8.6, P > 0.01) and a serum urea nitrogen concentration ≥16 mg/dl (χ² = 14.9, P > 0.001) were likewise predictive. To us, who have had the privilege of working with and clarifying this complex condition, it seems important to draw attention, again, to the critical value of simple, properly performed urinalysis in early diagnosis. For we believe that the prognosis for lupus nephritis in 1997 should be for the patient to experience a long life with good renal function after early detection and early effective treatment.

We would like to take this opportunity to thank our many fellows, colleagues, and friends who, over a period of more than 40 years in Chicago, Cincinnati, and New York, have collaborated with us in our work on The Natural History of the Renal Manifestations of Systemic Lupus Erythematosus. Their contributions and friendship are gratefully acknowledged.

GUEST COMMENTARY

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The advent of a new technical method often leads to the advancement of biomedical knowledge in several ways. New areas for study, previously inaccessible by existing techniques, are opened up. Deeper penetration into areas already under active study is facilitated, and our knowledge is expanded in areas where dogma has produced stagnation. The recent utilization of molecular biological and genetic techniques in both basic and clinical biomedical science is a case in point. The article by Pollak, Pirani, and Schwartz is an example of how the introduction of a new diagnostic technique produced new insights, cleared misunderstandings, and set the stage for all subsequent studies of renal disease. It is a milestone in that it demonstrates how the then newly developed technique of needle biopsy of the kidney contributed to our current understanding of the pathogenesis, natural history, and treatment of lupus nephritis.

A milestone is an indicator of the distance to or from a given point, just as this work marks the end of reliance on autopsy series and the beginning of the utilization of sequential data to map the natural history of renal disease. The article was written ten years after Kark and Muehrcke (1) modified the technique of aspiration biopsy of the kidney, which was introduced by Iverson and Brun (2), to make it a more practical tool for assessment of the morphologic consequences of renal diseases at several time points in the course of disease, rather than just at the end stage as viewed at autopsy. When Pollak joined Kark and Muehrcke, they put this technique to use in the study of lupus nephritis. They recognized the need for very careful histologic evaluation of the small amount of tissue obtained by needle biopsy and were able to recruit as the pathologist for their team,

1. There was no histologic evidence of renal involvement in 10 patients.
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3. Active lupus glomerulonephritis was diagnosed in the initial biopsy of 47 patients. In this condition the glomeruli were involved by a more severe proliferative and membranous process, frequently associated with necrotizing features, and there were definite tubular and interstitial changes. The lesions were usually pleomorphic, and a wide variety of individual abnormalities was seen in any single renal biopsy. Parts of each glomerulus were affected rather than whole glomeruli, and the lesions within the glomerulus were relatively local until a late stage. Many glomeruli were severely involved in some cases; severe involvement was focal in others. Local necrosis with obliteration of capillary loops, karyorrhexis, and fibrinoid changes usually affected some, but not all, of the glomeruli. These lesions occurred in association with areas of glomerular hypercellularity. Hematoxyphil bodies were found in some instances, hyaline thrombi more rarely, and on occasion a few polymorphonuclear leukocytes were seen in these areas. Reactive proliferation of visceral epithelial cells and later of the parietal cells of Bowman's
capsule occurred and led to fibroepithelial crescent formation and adhesions in some areas. Wire loop lesions, with fibrinoid on the endothelial side of the basement membrane, were seen frequently.*

4. Membranous lupus glomerulonephritis was found in the initial biopsy of 7 patients. The histologic findings differed from those in the 47 patients with active lupus glomerulonephritis, because diffuse thickening of the glomerular basement membrane and abnormalities of the tubules and interstitial tissue were the only lesions found. Changes in the basement membrane were very common in lupus glomerulitis and active lupus glomerulonephritis, but even when they were the dominant feature of the lupus glomerulitis and active lupus glomerulonephritis, tubules and interstitial tissue were the only lesions found. The histologic features of the glomerular changes did not appear to differ significantly from those observed in the idiopathic membranous glomerulonephritis, most commonly seen in patients with nephrotic syndrome and asymptomatic persistent proteinuria.10,11

Clinical and laboratory observations at the time of the initial renal biopsy. The age, sex, and race of the patients in each of the four histologic groups are given in Table III. At the time of the initial biopsy, no clinical differences were found between them in respect to the extrarenal manifestations of SLE. Thus, the incidence of arthritis and arthralgia, skin lesions, alopecia, leukopenia etc. were characteristic of SLE. Thus, the incidence of arthritis and other evidences of activity were not found. The histologic picture in the renal biopsies of these 7 patients was strikingly uniform, and hypercellularity, local necrotic lesions, wire loop lesions, and other indications of activity were not found. The histologic features of the glomerular changes did not appear to differ significantly from those observed in the idiopathic membranous glomerulonephritis, most commonly seen in patients with nephrotic syndrome and asymptomatic persistent proteinuria.10,11

The assembled team struck out into the new territory of careful clinical and pathological correlation. The clinicians in the group initially made the diagnosis of lupus erythematosus on the basis of the clinical findings, and the biopsies were analyzed separately by Dr. Pirani. They would all come together once a week, or even more frequently if necessary, to discuss an individual patient’s clinical and laboratory findings together with the histologic findings of the renal biopsy and, on the basis of all of the evidence, make a final decision as to whether lupus nephritis was the correct diagnosis. Their task was made somewhat easier with the advent of serological tests such as the assay of anti-nuclear factors, but it was this intense collaboration of clinician and pathologist in the management of the patient that was unique and which has set the pattern for the current-practice of nephrology. This approach led to an initial report published in 1957 and based on 33 patients (3), which demonstrated that the histological changes in various stages of lupus differed somewhat from the previous descriptions, which had been based solely on autopsy findings (4). They described a pleomorphic spectrum of renal lesions ranging from normal kidneys to lesions, which they described as lupus glomerulitis, membranous lupus nephritis, and active lupus glomerulonephritis. On the basis of this early study, which did not include serial biopsies, they concluded that lupus nephritis inevitably progressed from mild lesions to more severe lesions to produce a fatal glomerulonephritis in almost all patients within one to four years. It should be noted that during this same period, two additional milestones in renal medicine were being reached. The first was the empirical use of corticosteroids as a therapeutic anti-inflammatory agent in rheumatic diseases. The second, the application of advances in our understanding of immunology to the pathogenesis of renal disease in the publications of Dixon et al. (5) describing the pathogenesis of a laboratory model resembling the spectrum of human glomerulonephritis. It was in this environment that Pollak and Pirani, not satisfied with their initial static investigations, pressed forward to study patients with lupus nephritis over the long term, with serial biopsies and careful clinical follow-up. This continued effort resulted in this report of 87 patients with serial biopsies and with a follow-up ranging from seven months to eight years. Its publication resulted in several “firsts.” It is the first long-term follow-up study of lupus nephritis with serial biopsies: The first clear subcategorization of the renal lesions of lupus. The first semiquantitative assessment of the activity and chronicity of these lesions. The first well-documented correlation of clinical presentation with renal biopsy findings. And perhaps most important of all, the first retrospective study of the efficacy of high-dose corticosteroid therapy in this disease.

The results of this study clarified several misconceptions about lupus nephritis. It made the authors realize that their previous initial impression, based on static observations that

Table III. Pertinent clinical and laboratory findings at the time of the initial renal biopsy in 87 patients with SLE

<table>
<thead>
<tr>
<th>Histologic diagnosis in initial biopsy</th>
<th>No. of patients</th>
<th>Sex</th>
<th>Race</th>
<th>Serum creatinine (mg/100 ml)</th>
<th>Urea nitrogen (mg/100 ml)</th>
<th>Prognosis</th>
<th>Number of Nephrotic Syndrome</th>
<th>Mean and range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal kidney</td>
<td>28</td>
<td>1</td>
<td>27</td>
<td>1.0±0.22 13±7 2.4±0</td>
<td>0±0</td>
<td>19</td>
<td>0%</td>
<td>(29.54)</td>
</tr>
<tr>
<td>Lupus glomerulitis</td>
<td>23</td>
<td>2</td>
<td>21</td>
<td>1.0±0.22 15±7 3.7±4</td>
<td>4±1</td>
<td>19</td>
<td>0%</td>
<td>(14.48)</td>
</tr>
<tr>
<td>Membranous lupus glomerulonephritis</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>0.5±0.22 10±3 1.1±1</td>
<td>5±2</td>
<td>12</td>
<td>0%</td>
<td>(20.48)</td>
</tr>
<tr>
<td>Active lupus glomerulonephritis</td>
<td>47</td>
<td>57</td>
<td>30</td>
<td>1.0±0.28 10±5 3.0±1</td>
<td>12±6</td>
<td>13</td>
<td>0%</td>
<td>(18.55)</td>
</tr>
</tbody>
</table>

*Mean and range.

The average serum creatinine and urea nitrogen levels (Fig. 1) were within normal limits in patients with normal kidneys, with lupus glomerulitis, and with membranous lupus glomerulonephritis. In these 3 groups the average creatinine and urea clearances were within normal limits

*In its evolution, active lupus glomerulonephritis may go through stages of inactivity, barely spontaneously, more frequently as a result of treatment. Even in the inactive phase, the histologic pattern was sufficiently characteristic to be classified in this category, and no separate category of inactive lupus glomerulonephritis was deemed necessary.
or at the lower limit of normal. In patients with active lupus glomerulonephritis, the mean serum creatinine and urea nitrogen levels were elevated to 1.68 and 29.4 mg. per 100 ml. (median 1.25 and 20 mg. per 100 ml.), respectively, and the mean creatinine clearance was decreased to 66.3 ml. per minute (median 64.5 ml. per minute, range 7 to 156 ml. per minute).

Survival of the patients studied. The observations are summarized in Fig. 2.

Patients with normal renal biopsies. Of the 10 patients in whom the first renal biopsy was normal, 8 were alive at the time of the final assessment. Another had no renal involvement after 28 months, but her final status is not known. One patient died 2½ months after first study of miliary tuberculosis. At postmortem examination, there was no evidence of lupus nephritis. The living patients had been followed on an average of 71 months. With the single exception noted below, there was no subsequent clinical or laboratory evidence of renal disease or of deterioration of renal function in 9.

Four renal biopsies were made on subsequent occasions on 8 patients, and no histologic abnormalities were found. In one patient a second renal biopsy was normal 5 months after the first, when there was no clinical evidence of renal lupus nephritis was a continuum of disease that inexorably progressed, was wrong. The use of serial biopsies and long-term follow-up demonstrated that each of the different glomerular lesions had distinct clinical correlations and a separate natural history. The careful histological observations and separation into different categories of glomerular lesions based on histology was the first clear description of the protean manifestations of lupus in the kidney and provided the basis for the currently used WHO classification. Pirani also established criteria for assessing the relative activity and chronicity of the lesions he observed and set the standard for the currently used activity and chronicity indexes in more recent retrospective and prospective studies. This categorization of lesions and assessment of activity provided the basis for the better definition of clinical pathological correlation. Of the ten patients classified as normal and the 23 patients classified as lupus glomerulitis, only two showed progression to a more aggressive lesion. The seven patients with membranous lesions followed an indolent course, and none increased their activity during the follow-up. It was only in those patients who were categorized as active lupus glomerulonephritis, those who we would now call WHO Class III and IV, and who showed significant activity, that progression was seen. These were the patients who could benefit from treatment and who were treated with either low-dose or high-dose steroids. It is in this retrospective clinical trial that another milestone was achieved. This was the first demonstration that aggressive treatment with high-dose steroids could achieve a beneficial modulating effect on the clinical severity of disease, not only in preserving renal function but also in diminishing the activity of the morphologic lesion. This report of the efficacy of high-dose steroids in the treatment of lupus nephritis set the stage for the future prospective and retrospective studies of a variety of treatment regimens using cytotoxic and other immunosuppressive agents. The efficacy of any newer therapeutic approaches had to be compared against the "gold standard" of high-dose steroids advocated as a result of this study. Although not all of the patients benefited from the regimen of high-dose steroids, the findings were truly striking. Almost all of the patients with active lupus glomerulonephritis treated with low-dose steroids had renal death at the end of four years of follow-up, whereas only 50% of those treated with high-dose steroids showed evidence of progression in the same time period. It demonstrated that lupus nephritis could be successfully treated and inspired subsequent efforts to utilize steroid-sparing and -enhancing regimens that included cytotoxic agents.

Befitting the clarity of this clinical pathological study, these clinical investigators also looked to the advancements in the basic science of immunology achieved at that time for an explanation of their remarkable results. They drew upon the experimental work of Dixon and his coworkers (5) and postulated that their success in treatment was based on a modulation of the autoimmune response that altered the deposition of antigen-antibody
involvement. Proteinuria and abnormalities in the urine sediment were observed shortly after an exacerbation of SLE 18 months later, and mild active lupus glomerulonephritis was diagnosed histologically. She was treated with 40 mg. of prednisone per day for 5 months, when residual basement membrane thickening was found in the renal biopsy specimen, but without evidence of active glomerulonephritis. Now, 68 months since she first developed active lupus glomerulonephritis, there is no clinical evidence of renal disease except for slight proteinuria.

Patients with lupus glomerulitis. Of 23 patients in whom lupus glomerulitis was diagnosed in the first renal biopsy, 17 were alive at the final follow-up. One patient was not seen at the final follow-up but had been observed for 50 months, at which time she was in good health and had no evidence of renal disease. The average follow-up on these patients was 40 months. There was no evidence of progressive renal disease in any living patient at the time of the final study, and the serum urea nitrogen was 15 mg. per 100 ml. or less in 14 patients and 16 to 20 mg. per 100 ml. in the other 4. As there was little clinical evidence of progressive renal disease, renal biopsies were repeated on only 8 of these patients. The biopsy was normal in one patient; glomerulitis was found in a second. One patient developed mild active lupus glomerulonephritis following an exacerbation of acute SLE. She was then treated with large doses of steroids, and the progression of the renal disease was halted.

Three patients with lupus glomerulitis died of causes unrelated to their renal disease: one of accidental carbon-monoxide poisoning 8 years after the original study; a second of acute lupus myocardiopathy during an exacerbation of SLE. In both patients a second biopsy revealed only the changes of glomerulitis. A third patient died with subacute bacterial endocarditis 48 months after she was studied.

Two patients with lupus glomerulitis subsequently died in renal failure. In one, 4 biopsies over a period of 62 months showed evidence of glomerulitis only. Active lupus glomerulonephritis developed thereafter, her condition deteriorated, and she died in renal failure 67 months after she was first studied. The other patient presented with the nephrotic syndrome and SLE. The first renal biopsy done of her was classified as lupus glomerulitis, but there was evidence of active lesions. A second renal biopsy 6 months later showed inactive lesions of a similar nature. Twenty-two months after the first study, active lupus glomerulonephritis occurred in association with an exacerbation of SLE, and she died in renal failure 2 months later. Review of the initial renal biopsy revealed that the activity of the lesions, although mild, was more pronounced than in any other biopsy classified as lupus glomerulitis.

Patients with inactive membranous glomerulonephritis. All 7 patients with membranous glomerulonephritis associated with SLE were living an average of 44 months after initial study. The serum urea nitrogen level was less than 20 mg. per 100 ml. in all and less than 15 mg. per 100 ml. in 5. One patient developed massive proteinuria (8 to 10 Gm. per day) and the nephrotic syndrome. The amount of protein excreted in the urine in the other 6 patients was small, usually less than 1 Gm. per 24 hours. Six subsequent histologic studies were obtained in 5 patients. There was no significant change in any, and none developed histologic evidence of active lupus glomerulonephritis.

Patients with active lupus glomerulonephritis. By contrast, only 15 of 47 patients with active lupus glomerulonephritis were alive at the final assessment, an average of 34 months after the initial study. The serum urea nitrogen was 15 mg. per 100 ml. or less at the time of final follow-up in 9; it was between 16 and 20 mg. per 100 ml. in 4, and 21 to 25 mg. per 100 ml. in another 2. One patient was in renal failure (urea nitrogen 140 mg. per 100 ml.). Six patients died of causes unrelated to their renal disease: acute exacerbation of SLE; poliomyelitis; perforated esophagus; perforated peptic ulcer; and 2 apparently of septicemia. The other 26 patients died of renal failure. Heavy proteinuria was found in many of these patients, and the nephrotic syndrome was observed at some stage of the illness in 5 of the 15 living patients and in 25 of 32 patients who died. In fact, the nephrotic syndrome occurred in 23 of 26 patients who died in renal failure. Details of the histologic progression of the renal lesions in these patients will be given in the following section.
The effects of low and high doses of steroids on the clinical course of active lupus glomerulonephritis. Evidence has been published previously from this laboratory that treatment with large doses of prednisone for a prolonged period of time resulted in a significant increase in the life span of patients with lupus glomerulonephritis and that it did so by delaying the onset of renal failure. The data presented previously were from 26 patients with lupus glomerulonephritis. These observations were confirmed in the present analysis of 47 patients with active lupus glomerulonephritis. Sixteen of these were treated with small doses of steroids after active lupus glomerulonephritis was diagnosed by renal biopsy, and their status is compared with the response of 81 patients who were treated deliberately with large doses of prednisone after the histologic diagnosis of active lupus glomerulonephritis was made. Treatment was for an average of 6 months with 40 to 60 mg. of prednisone daily, irrespective of clinical symptoms. A second renal biopsy was done on most patients 6 months after treatment with large doses of prednisone was begun. The dosage of prednisone was then reduced gradually to lower levels for maintenance—e.g., 15 to 20 mg. per day—provided there was minimal or no evidence of activity in the renal biopsy done at this time.

The findings in Table III and Fig. 2 indicate that renal function was significantly worse initially in patients with active lupus glomerulonephritis than in any other group. At the time of the first histologic study there was no significant difference in serum urea nitrogen (Fig. 1), serum creatinine, or creatinine clearance between those patients with active lupus glomerulonephritis subsequently treated with small doses of steroids and those treated with large doses for 6 months. From the histologic point of view, the disease was considerably more severe in patients with active lupus glomerulonephritis than in other patients (Table II). A comparison of the initial renal biopsies of patients with active lupus glomerulonephritis indicated that the average severity of the lesions was the same for those treated subsequently with small or large doses of steroids, but the total glomerular damage and activity were slightly more severe in those treated subsequently with large doses of steroids.

Of the 16 patients in the low steroid group, 13 died of renal failure, two of nonrenal causes, and one is alive (Fig. 2). This patient, who had the mildest disease histologically, has survived 89 months without evidence of progression of the renal disease.

Twenty-five serial histologic studies were made on 18 of the 16 patients. In general, the lesions became more severe and histologic activity persisted (Figs. 3 and 4). Within the first year after the initial biopsy, the severity of the lesions was observed to increase in 10 patients, and there was no change in the other 8. Activity of the lesions was unchanged in 5, increased in 5, and decreased by one grade in 8. Histologic studies carried out over a longer period of time confirmed this pattern; the lesions gradually became more severe while activity persisted.

Of the 81 patients in the high steroid group, 18 died of renal failure, and 4 died of causes other than renal disease (Fig. 2). Fourteen patients were alive at the final follow-up, and only one was in renal failure. The average survival time was 31 months, the range being 7 to 74 months. The serum urea nitrogen level was less than 20 mg. per 100 ml. in 11 of those 14 patients and less than 25 mg. per 100 ml. in 18. One patient was in renal failure.

Serial histologic studies were made in 24 of the 31 patients (Figs. 3 and 4). There was less rapid progression of the severity of the lesions, and the activity of the lesions decreased to a greater degree than in the patients treated with low doses of steroids. Within the first year, the severity of the lesions was unchanged in 12 cases, increased in 4, and decreased in 8. The activity of the lesions was unchanged in 4 cases, had not increased in any, and had decreased by one or more grades in 19. Local necrosis, karyorrhexis, fibrinoid, hematoxyphil bodies, wire loop lesions, hyaline thrombi, and hypercellularity decreased or disappeared. Changes in the glomerular basement membrane, however, persisted in most cases. The histology did not revert to normal except in 2 instances, but a
similar or slightly more severe degree of basement membrane thickening in the glomerulus persisted. Interstitial fibrosis occasionally increased, though in many there was no progression of the interstitial process.

Previously we had noted that large doses of prednisone were effective in the treatment of active lupus glomerulonephritis, provided that the serum urea nitrogen level did not exceed 30 mg. per 100 ml. when the treatment was started. In 34 patients the serum urea nitrogen level was 30 mg. per 100 ml. of less. Of 18 patients treated with small doses of prednisone, only one survived. Of 21 treated with large doses of prednisone, 12 survived. The differences between the two groups is significant ($\chi^2 = 6.81$, $p = 0.02$). Only 2 patients in whom the serum urea nitrogen level exceeded 30 mg. per 100 ml. have survived, one presently being in renal failure. The percentage of patients dying from renal failure in each group is shown graphically in Fig. 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.](image)

Discussion

As a result of our earlier observations, we concluded that lupus glomerulitis was the earliest stage of involvement of the kidney by SLE and inferred that lupus glomerulitis progressed to lupus glomerulonephritis in a considerable proportion of patients. Now the natural history of the varying histologic types of renal involvement in lupus nephritis has been re-examined in a larger series of patients with the perspective of 8 years of follow-up studies.

Histologic abnormalities of the kidney have been reported in at least 75 per cent of patients with SLE on whom postmortem studies have been made. Clinical assessment of the incidence of renal abnormalities is difficult to make in patients with SLE, because lupus nephritis may occur without proteinuria or abnormalities in the urine sediment; and, per contra, proteinuria and urine sediment abnormalities may occur transiently in association with exacerbations of SLE and fever.

From the clinical point of view, however, most authors have pointed out that renal involvement is very common, varying in incidence from 62 per cent to 89 per cent. Histologically, there was no evidence of initial renal involvement in 10 of the 87 cases reported here. However, most of the patients studied were selected because of clinical evidence of renal involvement. From 1958 to 1955 renal biopsies were done on all patients with SLE, whether or not there was clinical evidence of renal abnormality. Six of 29 unselected patients (20 per cent) were found to have normal kidneys histologically—a figure similar to those found clinically by Harvey and associates and Soffer and associates.

Forty patients were studied for whom the initial histologic diagnosis was normal kidney, lupus glomerulitis, and membranous lupus glomerulonephritis. These 40 patients have been followed for a total of 160 patients-years—i.e., an average of 4 years per patient. During this period of time only one patient with healthy kidneys and only one with lupus glomerulitis developed lupus glomerulonephritis, which was mild, diagnosed early, and responded satisfactorily to treatment with prednisone. Two other patients with lupus glomerulitis subsequently developed lupus glomerulonephritis and died in renal failure. Thus, in an average 4 year follow-up period, progression from milder types of renal involvement to severe active lupus glomerulonephritis was an uncommon phenomenon.

From these observations it appears that lupus glomerulitis, with or without urinary abnormalities, does not necessarily represent an early stage of active lupus glomerulonephritis. Glomerulitis similar in degree has been observed in other diseases and could be a feature of a nonspecific generalized capillary response to various stimuli. Whether or not the type of glomerulitis seen in SLE is characteristic of this disease cannot be established in the absence of renal biopsy studies in a wide variety of acute systemic diseases.

In patients with SLE the finding of diffuse membranous glomerulonephritis without other glomerular lesions was unexpected, particularly since the glomerular lesions did not differ from those of idiopathic membranous glomerulonephritis. There was little clinical or histologic progression of the renal disease in these patients during the period of observation. In this respect it resembled the evolution of idiopathic membranous glomerulonephritis rather than that of active lupus glomerulonephritis. The reasons for the pattern of behavior of this type of nephritis in SLE are not clear. However, it should be emphasized that there was no significant differences in the incidence and type of extrarenal clinical and laboratory abnormalities in patients with membranous lupus glomerulonephritis and those with active lupus glomerulonephritis.

The many immunologic abnormalities which occur in SLE point to an immunologic basis for the nephritis of this disease and suggest that the glomerulus is the site of an antigen antibody reaction. As renal involvement occurred only in certain patients with SLE, whereas others with SLE of comparable severity remained free of sig-
significant renal disease for long periods of time, it is possible that there may be inherent differences between patients with SLE with and without nephritis; these differences could be related to the capacity of individual patients to produce antibody.

Several authors have confirmed the observation that the clinical course of active lupus glomerulonephritis is significantly altered by the use of large doses of prednisone.\(^{18,21-29}\) We have previously shown\(^7\) and now confirm that this effect is accompanied by a suppression of active lesions in the kidney. It is probably mediated through effective suppression of the immune response by large doses of prednisone.

The recent experiments of Dixon, Feldman, and Vazquez\(^{24}\) have introduced the possibility that circulating antigen-antibody complexes are in themselves damaging to the glomerulus. They observed 3 types of responses when rabbits were chronically immunized with heterologous serum protein. Animals which had a brisk immune response with large amounts of circulating antibodies developed only a transitory glomerulitis which disappeared spontaneously. Those animals in which the antibody response was less marked, so that antigen-antibody complexes were circulating continuously, developed glomerulonephritis. Animals with a poor antibody response did not develop any renal disease. These observations suggest that an immune response which is adequate to permit circulation of antigen-antibody complexes but inadequate to clear the antigen from the circulation may lead to glomerular lesions, irrespective of whether the antigen is directly related to renal tissue or not. It is intriguing to speculate on whether the three types of response in rabbits are analogous from an immunopathogenetic point of view to the response of the kidney in patients with SLE—i.e., transitory lupus glomerulitis, lupus glomerulonephritis, and SLE without renal involvement.

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