HISTOLOGICAL AND CLINICAL EVOLUTION OF LUPUS NEPHRITIS*†

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In recent years, lupus nephritis has become the major complication and the most pressing problem in patients suffering from lupus erythematosus disseminatus. The clinical course of the disease was different 15 years ago, when Keith (1940) wrote that "renal insufficiency does not play an important role in causing death". At that time patients usually died of a "lupus crisis" or as a result of concurrent infection. However, the use of antibiotics, blood transfusions, balanced water and electrolyte therapy, steroid hormone therapy, and injections of corticotropin has, apparently, prolonged life in those afflicted with systemic lupus erythematosus (S.L.E.). With present methods of care many such patients can usually be kept free of symptoms for a considerable length of time, only to succumb to a rapidly progressive renal failure.

Because of the problems raised by the increased incidence of lupus nephritis, a study of the histological evolution of renal involvement in S.L.E. was begun, using serial percutaneous renal biopsies (Kark and Muehrcke, 1954; Muehrcke and others, 1955a). Histological data were correlated with changing clinical status, clinical laboratory data, and renal function tests in a continuing study of the pathophysiology and natural history of lupus nephritis. Preliminary observations have been reported elsewhere (Pirani and others, 1954; Muehrcke and others, 1955b). This communication outlines some observations on 34 patients studied intensively during the past 18 months.

Methods

Selection of Patients.—34 patients with S.L.E. were studied from the medical services of three hospitals. The diagnosis was established in these patients by the characteristic findings listed in the Table. At least four clinical and four laboratory findings were present simultaneously in the same patient during the course of the illness, and most of the findings listed were present at some stage of the illness. Hargrave's cells (Hargraves and others, 1948) were found in the bone marrow or in the peripheral blood of thirty patients. In three of the four patients in whom Hargraves's cells were not found, histological study of the skin revealed findings compatible with L.E.

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Clinical and Laboratory Observations.—All patients were admitted to hospital for study and were followed in a special clinic. The following measurements were made on admission, and these studies were repeated from time to time:

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Urine analysis and urinary cultures; Haematogram, including examination for Hashem’s cells; Study of bleeding and clotting mechanism; Determination of serum protein and cholesterol levels; X rays of kidney; Standard urea and creatinine clearance tests; Measurement of 15 min. excretion of phenolsulphonephthalein; Specific gravity concentration test; Measurement of 24-hr excretion of urinary protein; Liver function tests, including measurement of serum cholinesterase; Measurement of blood urea nitrogen, non-protein nitrogen, and creatinine.

Discrete renal function tests were also done in a few patients.

**Percutaneous Renal Biopsies.**—These were done with the patient in a prone position. Details of the renal biopsy technique have been described elsewhere (Kark and Muehrcke, 1954; Muehrcke and others, 1955a).

The cylinder of renal tissue was divided into two portions. The first portion—a small piece of tissue—was placed in beef broth culture medium which was later examined for bacterial growth. The second and larger portion was fixed in 10 per cent. neutral formalin in saline. The sections were cut at 6 μ and stained with haematoxylin and eosin, periodic acid fuchsin, and Mallory stain. At times formalin fixed specimens were frozen, cut, and stained with oil-red-O for lipids.

A total of 61 percutaneous renal biopsies were done, usually when the patients were afebrile; 22 patients had serial renal biopsies. No serious complications followed the biopsies. All the cultures of biopsy tissue in beef broth were sterile. Six patients in whom biopsies had been done died later, and autopsies were done on three of them.

**Histological Evolution of Lupus Nephritis**

The earliest detectable histological lesions in the tissue were found in the glomeruli. These consisted of minute foci of hypercellularity at the periphery of the glomerular tufts (Fig. 1). These lesions were the result of endothelial cell proliferation and at times were associated with localized fibrinoid changes in the glomerular basement membrane. At this stage of lupus nephritis the tubules, blood vessels, and interstitial tissue were usually normal.

The early glomerular lesion was very similar in appearance to the lesions described by Stickney and Keith (1940). We have named this lesion “local glomerulitis” (Fig. 1). “Local”—because, initially, the lesion consisted of one or two patches of proliferating endothelial cells near the periphery of the tuft of some glomeruli. Eventually every glomerulus in the kidney became involved in this process. The term “focal glomerulitis” was not used to describe this lesion because it refers to a disease process which involves only a few glomeruli at any one time and never exists as a diffuse, widespread lesion involving all glomeruli.

As the patches of local hypercellularity in each glomerular tuft increased in size, the glomeruli became ischaemic, a few inflammatory cells appeared, and early necrotic changes and karyorrhexis were noted in the patch of cells (Fig. 2-A). As the local glomerulitis progressed, small fibrinous synechiae were seen bridging Bowman’s space (Fig. 2-B) and joining the glomerular tufts to Bowman’s capsule. Later, dense fibrous adhesions replaced the synechiae. These histological findings simulated the lesions of focal embolic glomerulonephritis (Fig. 2-A).

As the lupus nephritis progressed, the patchy areas of hypercellularity became more numerous and fused together to involve the whole glomerulus. More and more glomeruli became completely involved in the process. Eosinophilic thickening of the glomerular basement was also noted. Studies with periodic acid fuchsin stain indicated that this eosinophilic material was a mucopolysaccharide.

We have named the widespread involvement of glomerular tufts in the process of endothelial proliferation, the “general glomerulitis” stage of lupus nephritis (Fig. 3, opposite).

In some patients, the hypercellularity was the most prominent finding, while in others, fibrinoid thickening of the glomerular basement membrane was much more striking, and endothelial cell proliferation was less marked. This stage of local fibrinoid thickening of the glomerular capillary membrane is referred to as a “local membranous glomerulonephritis” (Fig. 4-A, overleaf).

Baehr, Klemperer, and Schifrin (1935) originally described this histological picture and named it the “wire-loop” lesion. However, we agree with Allen (1955) and Hass (1955) that the fibrinoid thickening of the glomerular basement membrane is more correctly named “membranous glomerulonephritis”.

We wish to emphasize that the advanced “wire-loop” lesions seen in patients with florid S.L.E. differ somewhat from the glomerular lesions seen in patients diagnosed as having membranous glomerulonephritis (Ellis Type II; Ellis, 1942). In lupus nephritis, the glomerular thickening was not uniform; fibrinoid changes were common in the glomerular endothelial membrane of lupus nephritis, and rare in Ellis Type II glomerulonephritis; patchy hypercellularity was a characteristic feature of lupus nephritis, but was usually not present in the glomeruli of Ellis Type II glomerulonephritis. A comparison of typical examples of these two lesions is shown in Figs 4-A and 5 (overleaf).
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Fig. 1.—Local glomerulitis in lupus nephritis.
Photomicrograph: Haematoxylin and eosin ×285.
A 32-year-old housewife had signs and symptoms of S.L.E. for 18 months before a small number of leucocytes and occasional granular and leucocyte casts were found in the urine. There was no proteinuria, and renal function tests were normal.
A renal biopsy revealed "local glomerulitis".
Note localized areas of hypercellularity, especially in periphery of glomerulus. Mild "fibrinoid" changes in the glomerular basement membrane can be seen within the areas of hypercellularity.

Fig. 2(a).—(June, 1954) Severe local glomerulitis simulating focal embolic glomerulonephritis.
Photomicrograph: Haematoxylin and eosin ×165.
A 12-year-old Negro school girl had signs and symptoms of S.L.E.; 11 months after admission to the clinic a trace of protein, numerous leucocytes, and a few casts were found in the urine. Renal function tests were normal. Study of the first renal biopsy (a) revealed severe "local glomerulitis". Note large area of hypercellularity with nuclear karyorrhexis within glomerular tuft. Moderate "fibrinoid" changes can be seen within glomerular basement membrane. This lesion simulates the histological picture of focal embolic glomerulonephritis.

Fig. 2(b).—(February, 1955) Local glomerulitis with adhesions.
Photomicrograph: Haematoxylin and eosin ×165.
A second renal biopsy was taken 6 months later when the patient had developed the nephrotic syndrome. Gross proteinuria, doubly refractile bodies, and numerous fatty, hyaline, and granular casts were found in the urine. Note local hypercellularity in glomerular tuft, irregular "fibrinoid" thickening of glomerular basement membrane, and adhesion between glomerular tuft and Bowman's capsule.

Fig. 3.—General glomerulitis.
Photomicrograph: Haematoxylin and eosin ×280.
A 23-year-old Negro woman was ill with S.L.E. for 2 years. A trace of protein, a few leucocytes, and hyaline casts were found in the urine. Renal biopsy disclosed "general glomerulitis". Note diffuse hypercellularity of glomerular tuft, no significant changes in glomerular basement membrane or in Bowman's capsule.
Fig. 4(a).—(September, 1954) Local membranous glomerulonephritis ("wire-loop" type).
Photomicrograph: Haematoxylin and eosin x 200.
A 22-year-old Negro woman had had florid S.L.E. for slightly less than 2 years, when gross proteinuria, several leucocytes, and leucocyte and granular casts were found in the urine. Renal functions were markedly impaired. The first renal biopsy disclosed "local membranous glomerulonephritis". Note marked local "fibrinoid" thickening of glomerular basement membrane simulating wire loops. The glomerulus is lobulated and ischaemic. General mild hypercellularity can be seen.

Subacute glomerulonephritis was commonly found in patients with lupus nephritis. These lesions developed as early as 2 months after the "wire-loop" stage of lupus nephritis (Fig. 4-B) and were usually found in biopsy material from patients with S.L.E. who had the nephrotic syndrome.

Fig. 4(b).—(November, 1954) Subacute glomerulonephritis.
Photomicrograph: Haematoxylin and eosin x 200.
Two months later the patient became uraemic. Her blood pressure increased to 180/112 mm. Hg, and she died of pulmonary oedema and renal failure. At autopsy the kidneys were large, swollen, and pale. Histological examination revealed typical subacute glomerulonephritis.

Note large fibro-epithelial crescent in Bowman's space. The glomerular tuft is lobulated, contracted, and moderately hypercellular. An area of local hypercellularity can also be seen at the periphery of the glomerular tuft.

This stage of lupus nephritis was characterized by ischaemic, moderately hypercellular glomeruli which "wire-loop" lesions might or might not be detected. In addition, fibro-epithelial crescents in Bowman's capsule were seen in many glomeruli which were compressed and reduced in size. Usually the convoluted tubules were moderately degenerated.
Within the interstitial tissue, moderate to severe oedema was noted, and this was usually associated with the presence of chronic inflammatory cells.
In three patients, the lesions of chronic glomerulonephritis (Fig. 6-B) were found in the renal biopsy tissue. These lesions and those described above under "subacute glomerulonephritis" were typical of those seen in Ellis Type I glomerulonephritis (Fig. 6-A). Nevertheless, we have observed the progression of "wire-loop" lesions (local membranous glomerulonephritic stage of lupus nephritis) to typical subacute glomerulonephritis (Fig. 6-A), which could not be distinguished from the lesions of the Ellis Type I.

Thus far, renal insufficiency has been the cause of death in all the six patients from our biopsy series who have died; and in each of these patients the kidneys were severely damaged, either with local membranous glomerulonephritis or with typical lesions of subacute glomerulonephritis. It has been stated that kidneys in patients with lupus nephritis are normal or enlarged (Allen, 1951; Baggenstoys, 1952), and in general we agree with this statement.
In 35 autopsied cases of S.L.E. which we have...
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A 21-year-old youth was ill with S.L.E. for one year before he developed the nephrotic syndrome. The first renal biopsy was taken 4 months after the onset of oedema when renal function was moderately impaired. Large kidneys were seen on x ray. The histological diagnosis was the subacute glomerulonephritic stage of lupus nephritis. Note diffuse hypercellularity of glomerular tufts which are adherent to Bowman’s capsule in many areas, marked epithelial cell proliferation of Bowman’s capsule, tubular atrophy, and interstitial fibrosis can be seen.

Eight months later the patient had developed hypertension (blood pressure: 170/115 mm. Hg) and his renal function was markedly impaired. Small kidneys were seen on x ray. The histological diagnosis was the chronic glomerulonephritic stage of lupus nephritis. Note partial hyalinization of glomerular tuft and contraction of glomerulus. The tubular atrophy and interstitial fibrosis are more severe than in (a).

Pseudo-Nephrotic Syndrome and Nephrotic Syndrome associated in Lupus Nephritis

In our series of 32 patients with lupus nephritis, five developed the nephrotic syndrome. The clinical and laboratory findings in these patients fulfilled the criteria set forth by Leiter (1931). All five patients had had a facial rash early in their disease, but none of them had the rash at the height of the nephrotic syndrome. This change has been commented on previously (Brenner and others, 1948). Three other patients ill with lupus nephritis were admitted with the clinical features of the nephrotic syndrome; these were unusual because the serum levels of cholesterol and cholinesterase were extremely low, despite the finding of doubly refractile bodies in the urine. Their clinical course was also

studied, not a single “contracted kidney” was found.

However, in one of our patients, presently ill with lupus nephritis and with histological evidence of chronic glomerulonephritis on biopsy, the kidneys were found to be small on x ray of the abdomen.

“Wire-loop” lesions and haematoxylin bodies were not commonly seen. Typical “wire-loop” lesions were found in only four of 61 biopsies. In reviewing renal tissue from 35 autopsied cases of S.L.E., none of whom had been biopsied, “wire-loop” lesions were found in nine patients. In view of the discrepancy between our biopsy data and the finding of Klemperer and others (1941) of a high incidence of “wire-loop” lesions in S.L.E., one can speculate that “wire-loop” lesions exist only as a stage of renal involvement in this disease, appearing between the early and the late manifestations of lupus nephritis. If this speculation were true, it would mean that “wire-loop” lesions were transitory and short-lived. Another explanation is that “wire-looping” may be an expression of the severity of the fibrinoid reaction which is so characteristic of S.L.E. In the pre-steroid therapy days, patients with S.L.E. died in “lupus crisis”, and massive fibrinoid changes commonly occurred (Keith, 1940; Muehrcke and others, 1955c). Nowadays, steroid therapy appears to suppress the basic disease reaction which produces or results in severe fibrinoid changes. Unfortunately, steroid therapy does not prevent the progression of local glomerulitis to the general glomerulitis stage of lupus nephritis and further progression of this latter lesion to chronic glomerulonephritis. We are certain that local glomerulitis is not the result of cortisone therapy, because this lesion was commonly found in the kidneys of patients with S.L.E. before ACTH or steroid therapy was introduced (Stickney and Keith, 1940). Whether steroid or ACTH therapy aggravates lupus nephritis in man once the lesion develops in the kidney is not known. This is a clinical point for further investigation, as animal studies indicate that administration of ACTH or steroids may produce or aggravate experimentally-induced glomerulonephritis (Teilum and others, 1951; Bloodworth and Hamwi, 1955).

Fig. 6(a).—Subacute glomerulonephritis (lupus nephritis). Photomicrograph: Haematoxylin and eosin × 165.

Fig. 6(b).—Chronic glomerulonephritis (lupus nephritis). Photomicrograph: Haematoxylin and eosin × 165.
unusual, as they developed rapid progressive renal failure and died within 2 to 4 months after the oedema first appeared. Histological findings were also different from those seen in the group of five patients with typical nephrotic syndrome, as hyaline thrombi, marked fibrinoid changes, and severe inflammatory reaction were observed (Fig. 7). Because of the unusual clinical, laboratory, and histological features presented by these three patients, we have grouped them together as cases of the "pseudo-nephrotic syndrome".

**Correlation between Urine Analysis, Renal Function and Renal Histology**

Preliminary study of our data shows that a correlation exists between urine analysis, tests of renal function, and histological findings in the kidney. With the earliest lesion—local glomerulitis—the urine often mimicked that found in pyelonephritis; that is, the specific gravity was normal; one plus proteinuria was present, and the urinary sediment contained many white blood cells, a few red blood cells, and a few casts. The P.S.P., urea clearance, and blood pressure were within normal limits.

By the time subacute glomerulonephritis developed, the urine specific gravity had fallen (ranging between 1.017 and 1.022), massive proteinuria was present, and numerous casts were seen, including fatty casts and doubly refractile bodies. The 15-min. P.S.P. excretion test ranged between 13 and 22 per cent, and the urea clearance also fell. The blood pressure was normal and did not rise until chronic glomerulonephritis developed. In this late stage of lupus nephritis the specific gravity was fixed, four plus proteinuria was noted, and few cellular elements were seen on microscopic examination. However, some broad casts were found. Renal function was severely depressed at this stage of the disease.

**Summary**

The histological evolution of lupus nephritis was studied in 32 patients with systemic lupus erythematous by percutaneous needle biopsy, and 22 of the patients had serial renal biopsies. Histological data were correlated with the changing clinical status, laboratory data, and renal function tests.

The earliest glomerular involvement was a local glomerulitis characterized by local hypercellularity and occasionally by fibrinoid changes. Glomerular...
lesions progressed from local glomerulitis, through general glomerulitis, to subacute glomerulonephritis. In the biopsy material, "wire-loop" lesions were rarely seen and appeared to represent a transitory stage in the development of lupus nephritis.

There were two distinct groups of oedematous patients with lupus nephritis: one had the clinical and laboratory features of the nephrotic syndrome; the second had a pseudo-nephrotic syndrome associated with low serum levels of cholesterol and cholinesterase. Their illness progressed rapidly to its termination, and they died in renal failure a few months after oedema appeared.

Urine analysis correlated with renal pathology. White blood cells and white blood cell casts were found with local glomerulitis. Mild proteinuria was associated with general glomerulitis. Impairment of renal function was observed with subacute glomerulonephritis. Hypertension and a fixed specific gravity accompanied chronic glomerulonephritis.

This study demonstrated the value of correlating the progression of histological changes with the concomitant clinical and laboratory data in observing the natural history of a disease.

REFERENCES

Evolution clinica e histol6gica de la nefritis luposa

SUMARIO
Se estudi6 la evoluci6n histol6gica de la nefritis en 32 enfermos con lupus eritematoso generalizado por medio de biopsias por puncci6n percut6nea y en 22 de ellos por medio de biopsias renales seriadas. Los datos histol6gicos fueron considerados en relaci6n con las alteraciones cl6nicas, de laboratorio y de la funci6n renal.

El compromiso glomerular iniciaba con una glomerulitis local caracterizada por una hipercelularidad local y, a veces, con alteraciones fibrinoides. Luego, la glomerulitis se generalizaba acabando con una glomerulonefritis subaguda.

Hubo dos grupos distintos de enfermos edematosos con nefritis luposa: uno con los rasgos cl6nicos y de laboratorio del sindrome nefr6tico y el otro con el sindrome seudo-nefr6tico asociado con cifras sericas bajas de colesterol y de colinesterasa. La enfermedad de estos progresaba rapidamente hacia la muerte poquisimos meses desp6s del comienzo del edema.

Los hallazgos en la orina correspondian a las lesiones renales. Leucocitos y cilindros aparecian con la glomerulitis local y un poco de albumina con la glomerulitis generalizada. Una mejoria de la funci6n renal se observava en el curso de la glomerulonefritis subaguda. La glomerulonefritis cronica se acompanaba de hiper-tension y de densidad fija.

Este estudio demuestra el valor de la correlaci6n del progreso de las alteraciones histol6gicas con los datos cl6nicos y de laboratorio concomitantes al observar la historia natural de una enfermedad.