HISTOLOGICAL AND CLINICAL EVOLUTION OF LUPUS NEPHRITIS*†

BY

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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.

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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. Hargraves'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 Har-greaves'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 phenolsulphonephthalain;
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 synchiae 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 a 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 focal 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).
HISTOLOGICAL AND CLINICAL EVOLUTION OF LUPUS NEPHRITIS

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.
This stage of lupus nephritis was characterized by ischaemic, moderately hypercellular glomeruli in which “wire-loop” lesions might or might not be detected. In addition, fibro-epithelial crescents of 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 membranous 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; Baggenstoss, 1952), and in general we agree with this statement.

In 35 autopsied cases of S.L.E. which we have

Fig. 4(a).—(September, 1954) Local membranous glomerulonephritis (“wire-loop” type).
Photomicrograph: Haematoxylin and eosin ×200.
A 22-year-old Negro woman had had flroid 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.

Fig. 4(b).—(November, 1954) Subacute glomerulonephritis.
Photomicrograph: Haematoxylin and eosin ×200.
Two months later the patient became uremic. 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.

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In 35 autopsied cases of S.L.E. which we have

Fig. 5.—Chronic membranous glomerulonephritis (Ellis Type II).
Photomicrograph: Haematoxylin and eosin ×275.
This typical example of chronic membranous glomerulonephritis (Ellis Type II) should be compared with the local membranous glomerulonephritis of lupus nephritis (see Text).
A 44-year-old taxicab driver developed the nephrotic syndrome in 1953. Detailed clinical and laboratory studies indicated Ellis Type II membranous glomerulonephritis. Note marked, diffuse thickening of glomerular basement membrane which is dense. The homogeneous hyaline thickening of the membrane differs from the granular clotted appearance of “fibrinoid” thickening.

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.
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. 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).

**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 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
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 erythematosus by percutaneous needle biopsy, and 22 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.

Figure 7.—Localised membranous glomerulonephritis ("pseudo-nephrotic" stage of lupus nephritis).

Photomicrograph: Haematoxylin and eosin × 330.

An 18-year-old girl developed signs and symptoms of S.L.E. in July, 1954. One month later, oedema of the legs, face, and eyelids appeared. Gross proteinuria and numerous fatty, hyaline, and cellular casts were found in the urine.

In October, 1954, she developed uraemia and hypertension (blood pressure: 160/110 mm. Hg); the oedema persisted. The levels of serum cholesterol and cholinesterase were reduced. The patient died as a result of renal failure soon after the biopsy was taken.

The histological diagnosis was the local membranous glomerulonephritic stage of lupus nephritis. Note irregular "fibrinoid" thickening of glomerular basement membrane which is very broad in some areas. The glomerulus is ischaemic but not hypercellular. A hyaline thrombus is seen within one capillary lumen (arrow). The interstitial tissue is markedly oedematous and contains chronic inflammatory cells.
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 histologica de la nefritis luposa

SUMARIO

Se estudió la evolución histológica de la nefritis en 32 enfermos con lupus eritematoso generalizado por medio de biopsias por punción percutánea y en 22 de ellos por medio de biopsias renales seriadas. Los datos histológicos fueron considerados en relación con las alteraciones clínicas, de laboratorio y de la función renal. El compromiso glomerular iniciaba con una glomerulitis local caracterizada por una hipercelularidad local y, a veces, con alteraciones fibrinoideas. Luego, la glomerulitis se generalizaba acabando con una glomerulonefritis subaguda. En los fragmentos de biopsia se vieron pocas lesiones del tipo "asa filiforme" (wire-loop); estas parecen representar una etapa transitoria en la evolución de la nefritis luposa.

Hubo dos grupos distintos de enfermos edematosos con nefritis luposa: uno con los rasgos clínicos y de laboratorio del síndrome nefrótico y el otro con el síndrome seudo-nefrótico asociado con cifras séricas bajas de colesterol y de colinesterasa. La enfermedad de éstos progresaba rápidamente hacia la muerte poquirénicos meses después del comienzo del edema.

Los hallazgos en la orina correspondían a las lesiones renales. Los leucocitos y células morfológicas aparecían con la glomerulitis local y un poco de albumina con la glomerulitis generalizada. Una mejoría de la función renal se observaba en el curso de la glomerulonefritis subaguda. La glomerulonefritis crónica se acompañaba de hiperterensión y de densidad fija.

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

Evolution clinique et histologique de la néphrite compliquant le lupus érythémateux

RÉSUMÉ

On étudia l'évolution histologique de la néphrite chez 32 malades atteints de lupus érythémateux généralisé à l'aide de la ponction percutanée et chez 22 d'entre eux des biopsies rénales en série. Les données histologiques furent considérées à la lumière de l'évolution clinique, des résultats de laboratoire et des résultats des épreuves de la fonction rénale.

La première atteinte glomérulaire fut une glomérulite locale caractérisée par l'hypercellularité locale et, quelquefois, par des alterations fibrinoidees. De là, la glomérulite tendait à se généraliser, évoluant vers la glomérulonephrite subaguée. Dans le matériel prélevé on ne vit que rarement des lésions à "l'anse filiforme" (wire-loop) qui semblent représenter un stade transitoire de l'évolution de la néphrite lupique.

Parmi les malades oédemateux atteints de néphrite lupique il y avait deux groupes distincts: l'un présentait des caractères cliniques et de laboratoire du syndrome néphrotique; chez l'autre le tableau du syndrome pseudo-néphrotique était accompagné d'un taux sérique bas de cholestérol et de cholinésterase. Leur maladie évoluait rapidement vers la mort d'insuffisance rénale peu de mois après le début de l'œdème.

L'état de l'urine correspondait aux lésions du rein. Au stade de glomérulite locale on trouvait des leucocytes et des cylindres et au cours de la glomérulonephrite subaguée. La glomérulonephrite chronique s'accompagnait d'hypertension et de densité constante.

Ce travail montre la valeur de l'étude comparée des altérations histologiques progressives et des données cliniques et de laboratoire concomitantes quand on observe l'histoire naturelle d'une maladie.

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