

LUPUS NEPHRITIS

By

Robert C. Muehrcke, MS, MD

*Postdoctoral Public Health Fellow in Internal Medicine Research and Educational Hospitals University of Illinois College of Medicine Chicago
Assistant Chief of Hospital Research Fellow Medical College of Chicago Hospital Chicago*

Robert M. Kark, FRCP, FACP

*Professor of Medicine University of Illinois College of Medicine Chicago
Physician, Research and Educational Hospitals and Clinics of the University of Illinois
Associate Attending Physician Jefferson Hospital Chicago*

Conrad L. Pirani, MD

Professor of Pathology University of Illinois College of Medicine Chicago

Victor E. Pollack, MB, MRCPE

*Research Fellow in Medicine Presbyterian Hospital Institute of Medicine
University of Illinois College of Medicine Chicago*



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I INTRODUCTION

Lupus Nephritis describes succinctly and graphically involvement of the kidney in Systemic Lupus Erythematosus (SLE). Etymologically, the term lupus nephritis is far from perfect, since it combines a Latin and a Greek word to describe a clinical and pathologic entity. Descriptively it is inaccurate for the face and skin of those who are ill with lupus nephritis have neither the nature nor the qualities of a scarred wolf-bite.

Although we have coined ponderous but precise phrases to describe the grave but common renal complications of SLE the words "lupus" and "nephritis" have the virtue of common usage, and this consideration overrides all other aspects of nomenclature. 'Lupus nephritis,' thus named, serves to focus attention on a specific disease of the kidney which is at present the major complication and the most pressing problem in patients ill with SLE. The clinical course of the disease was different fifteen years ago when Keith (140) wrote, '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 infection

(92-176) However the introduction and liberal use of antibiotics blood transfusions balanced water and electrolyte therapy and corticotrophin (ACTH) and steroid hormone therapy have apparently prolonged life in those afflicted by SLE. With present methods of care many patients with SLE can usually be kept free of symptoms for a considerable length of time only to succumb to a progressive renal failure.

Because of the problems raised by the increased incidence of lupus nephritis a study of the renal involvement in SLE was undertaken. The use of serial percutaneous renal biopsies (133-199) enabled us to follow the histological evolution of kidney involvement. The changing clinical status laboratory data and renal function tests were correlated with the serial pathological changes. Thus a continuing study of the pathophysiology and natural history of lupus nephritis was possible. Preliminary observations have been reported elsewhere (201-202-226). This communication outlines observations on thirty-three patients studied intensively during the past two years and was supplemented by a retrospective study of twenty-one cases collected from the post mortem material in the hospitals. Departments of Pathology.

II REVIEW OF CLINICAL FEATURES

I INTRODUCTION

Lupus erythematosus was first recognized over 120 years ago. In 1827 Peyer (236) described it as a rare form of flux sebacee. Eleven years later Biett (27) writing in Cazenave and Schedel's textbook called it erytheme centrifuge and described: Dartre rongeante qui detruit en surface. In 1863 Fuchs (83) called it scborrhagia adultorum. There seems little doubt that these diseases are identical with what we know today as lupus erythematosus. I dated observations were reported by other authors. It was named hypertrichia folliculorum by Robert Wilks (302) inflammatio folliculorum by Erasmus Wilson (303) stearrhœa flavescens by Neligan (205) and acut. sebacea by Erichsen (76).

F Hebra (116) and Cazenave (49-50) first outlined the disease clearly and distinctly. In 1845 Hebra (116) described it under the name sciorrhœa congestive. In 1856 in his classic *Atlas der Hautkrankheiten* (116) he depicted two forms of the disease and used the term lupus erythematosus—first coined by Cazenave (48) in his fundamental work of 1801. Neumann (206) in 1863 described the pathology of the skin lesion in this disease.

Kaposi (132) in 1872 suggested that there were two forms of the disease and named them lupus erythematosus disseinles and lupus erythematosus discretus et aggregatus. In the course of his pathological studies (117-132) he observed specific changes in the connective tissue of the papillary layer of the skin. These changes he called hyaloid degeneration. Five years later Neumann (207) introduced the term fibrinoid degeneration to describe the change in the collagen fibers which assumed the same staining and structural qualities as fibrin.

2 RENAL INVOLVEMENT IN SLE

At the turn of the century renal involvement was recognized in cases reported by Hallopeau (106) Cayafy (47) Galloway and MacLeod (86 175) Little (171) and Short (261) In 1895 Brooke (36) found all the signs of soft white kidneys at the post mortem examination of a woman ill with lupus erythematosus and proteinuria Sequerra and Bilean (256) reported ten cases of lupus erythematosus and noted involvement of the kidneys in five Galloway and MacLeod (86) in 1903 and Jadaohn (122) also stressed the frequent affection of the kidneys

Sir William Osler in a number of publications (213 214 215 216 217 218) described the systemic manifestations of a group of diseases which involved the skin and joints His first papers in 1888 (213) and 1895 (214) described cases of Henoch Schonlein purpura By 1904 (216 217) he had described twenty nine patients Only one case a fifteen year old girl fulfilled our criteria for SLE She died in uremia (Case 19) This is the first American description of a case of SLE However Osler did not distinguish this case from others with the

Erythema Group of Skin Diseases (214) and it is incorrect to attribute to him recognition of SLE as Tumulty and Harvey have done (291) In his review of Henoch Schonlein purpura Gardner (84) correctly pointed out that in these papers Osler had delineated the clinical features of Henoch Schonlein purpura²

In 1908 Pernet (222) described a case of lupus erythematosus with a rapid and fatal course Protein was found in the patient's urine He collected nine similar cases from the literature and called this group lupus erythematosus rugidum In 1922 Keith and Rowntree (141) reported four patients with lupus erythematosus and nephritis and stressed that nephritis was a common complication of disseminated lupus erythematosus Two years later Libman and Sacks (167) reported the clinical syndrome produced by the atypical verrucous endocarditis of SLE which bears their name They found that there was histologic evidence of renal disease in three of their four patients one of whom died in uremia Baehr (8) in 1931 reported renal complications in seventeen cases of Libman Sacks disease He concluded that the lesions were an expression of

importance of renal involvement in lupus erythematosus and stated that therapeutic measures have had no beneficial effect Dargatzis and Bagge (63) reported seven cases of Libman Sacks disease who had nephrotic edema arthritis of varying duration and a rapidly progressive course These patients none of whom had a face rash died in renal failure In 1954 preliminary studies of serial renal biopsies in SLE were reported by Muehrcke Kark and Pirani (201 202 226) and Lister and Baker (170) reported a case of SLE diagnosed by renal biopsy

²We wish to thank Dr W W Francis and Dr Lloyd Stevenson of the Osler Library McGill University Montreal for access to Osler's personal papers manuscripts and books

3 URINARY FINDINGS

Protein and formed elements may appear in the urine in patients with SLE when they are acutely ill, dehydrated and febrile (110, 269). As in other conditions these abnormal urinary findings may be transitory. For this reason the exact interpretation of data on urinary findings reported by previous authors is difficult, as one is often uncertain as to the permanency and significance of their observations on the urine.

On the basis of abnormal urinary findings Montgomery and McCreight (191) reported renal irritation, nephrosis or nephritis in 100% of thirty-two cases of acute SLE and in 69% of seventy-seven cases of subacute SLE. Other authors reported that abnormal urinary findings were usually transitory during acute exacerbations. The abnormalities disappeared either when spontaneous remission occurred (273) or as a result of therapy (42, 110, 269). However, if urinary abnormalities persisted during the stage of remission, then renal damage usually was permanent. Ross and Wells (248), who studied thirty-four patients with SLE, wrote: "Abnormal urinary findings are so common that in their absence we may justifiably question a diagnosis of lupus erythematosus." However, Harvey and his colleagues (110) found no evidence of renal disease in 26% of their 138 patients with SLE.

Considerable amounts of protein may be found in the urine during acute exacerbations of SLE (140) and Madden (176) felt that persistent proteinuria was of prognostic value as it was found more frequently in the fatal cases. Gross hematuria was observed in 6% of 34 cases reported by Shearn and Pirofsky (209) and Soffer (269) reported that microscopic hematuria was often found during acute exacerbations. Erythrocytes, leucocytes and casts were found in the urine at some stage in the course of SLE in 64% of 44 cases observed by Jessar and his colleagues (127) and in 56% of 279 cases reviewed by them. Fishberg (78) observed that clumps of leucocytes were common; this finding has led clinicians to make an erroneous diagnosis of pyelonephritis. Krupp (158) found a telescoping of the urinary sediment in four patients with lupus erythematosus. This telescoped urinary sediment contained elements representing the three stages of glomerulonephritis—the erythrocyte and erythrocyte casts found in the acute stage, the oval fat bodies and fatty casts of the subacute stage and the broad casts found in chronic glomerulonephritis.

Krupp's observation was confirmed by Mirle (185) but Cole (56) reported identical urinary findings in a case of polyarteritis nodosa and Schreiner (205) noted telescoped urinary findings in three proven cases of chronic glomerulonephritis. He pointed out that although the finding of telescoped urinary

Vural (102) attempted to correlate urinary findings with renal pathology in a retrospective study of 20 patients who died of SLE. They found no correlation of urinary abnormalities with the histologic appearance of the kidneys.

4 RENAL FUNCTION

Ad quite studies of renal function have been made but rarely (190) Soffer, Iudemann and Brill (269) studied renal function in slightly more than half of their 55 patients with acute SLE and considered that the urine concentration test was the least sensitive of the renal function tests they used. They stated that the 15 minute excretion of phenolsulphonphthalam and the urea clearance test yielded the most useful information in assessing the function of the kidney in SLE. Azotemia was present in 16% of their patients and was also found in 16% of 216 cases reviewed by Jassar *et al* (127). Soffer and his colleagues (269) observed an elevation of the blood urea nitrogen level in over one third of patients in whom protein or erythrocytes were found in the urine. Azotemia was usually progressive and death from renal insufficiency resulted. They believed that persistent azotemia was a serious prognostic sign (266).

5 EDEMA AND THE NEPHROTIC SYNDROME

Jassar and his colleagues (127) reviewed the literature on SLE which was published between 1948 and 1952. They found reports of 279 patients and added 44 of their own which had been studied between 1937 and 1952—a total of 323 cases. Edema was noted in approximately 16% while Soffer, Iudemann and Brill (269) found edema in 22% of the 55 patients they studied.

In 1939 Reifenstein and his colleagues (237) reviewed 17 cases of SLE reported in the literature and added one of their own. Retrospectively they diagnosed the nephrotic syndrome in two of these patients. We cannot agree that there was sufficient evidence in either case to warrant a diagnosis of nephrotic syndrome. The first patient had been reported by Belote and Ratner (21), who found protein and casts in the urine. The patient was not edematous and the levels of serum albumin and cholesterol were not recorded. Tubular nephrosis was diagnosed at autopsy. The second case was reported originally by Tremaine (289) and although the patient had features of the nephrotic syndrome (edema, proteinuria, hypoalbuminemia) the serum cholesterol level was not elevated. Six weeks after the onset of edema the patient died. Histologic examination revealed severe glomerular and tubular damage. Shearn and Pirofsky (259) noted that four of their patients had a clinical variant of the nephrotic syndrome. A post-mortem examination of two disclosed chronic glomerulonephritis. Three of the four patients had serum cholesterol levels within the range of normal and in the fourth an initial level of 420 mg/100 ml later decreased to 250 mg. This patient was reported in full by Brunner and his colleagues (35) as a case of nephrotic syndrome. Drugherty and Biggen-toss (63) observed seven cases with nephrotic edema, arthritis of varying duration, marked proteinuria and with a rapidly progressive course. Subacute glomerulonephritis was found in three and chronic glomerulonephritis in one of the four cases on whom autopsies were done.

Bossik and Adlersburg (33) studied the biochemical features of the nephrotic syndrome in a patient ill with SLE. They found azotemia, low serum proteins, normal alpha 2 globulin, raised beta globulin and a marked rise in gamma globulin levels. The levels of total lipid and neutral fat were greatly increased.

the beta lipoprotein was decreased and the cholesterol and phospholipid levels were slightly elevated

6 HYPERTENSION

Hypertension is said to appear late in the course of SLE—usually in the presence of advanced renal disease (102-110). The incidence of hypertension associated with SLE varied from 9% to 214 cases (127) to 12% of 138 cases (110). In more than half of Harvey's patients (110) who had hypertension renal involvement was so severe that nitrogen retention had developed. On the other hand blood pressure had always been normal in five patients who died in uremia. Soffer and his colleagues (269) reported hypertension in 13% of 55 patients and found that treatment with cortisone and ACTH was not effective in reducing blood pressure levels.

III REVIEW OF RENAL PATHOLOGY

I INTRODUCTION

In the past twenty years Klemperer, Baehr and their colleagues have made the most thorough pathologic studies of SLE. In 1941 they thought (151) that the changes occurring in collagenous tissues were primarily degenerative in nature. They observed differences between SLE and rheumatic fever. In rheumatic fever proliferation of fibroblasts was the main feature frequently resulting in Aschoff body formation. In SLE on the other hand degeneration of collagen was the predominant histologic finding and the cellular reaction was not a prominent feature (144). In distinguishing between SLE and polyarteritis nodosa they pointed out that in SLE degenerative changes appeared in the small vessels and capillaries while vessels of a larger caliber were usually affected in polyarteritis nodosa. The changes in the connective tissues in polyarteritis nodosa were also accompanied by an inflammatory reaction associated with an infiltration of eosinophilic polymorphonuclear cells. These changes were not seen in SLE.

It is apparent from reading their publications that Klemperer and his colleagues modified their opinions in the course of their studies on the so-called systemic 'collagen diseases'. They came to regard the widespread alterations in the connective tissues as a manifestation of a single process involving not collagen but the ground substance of the heart, glomeruli, the skin and the blood vessels (148). Histochemical studies by Klemperer's associates Gueft and Jaffer (104) indicated that the fibrinoid material seen in the ground substance in SLE includes an unusual protein derived from the degradation of nuclear proteins. This protein was later characterized as a paraprotein which appeared as a result of the metabolic defect in SLE (147-148). Klemperer and his co-workers suggested that the paraprotein impregnated the ground substance by translocation from the bloodstream into the vessel wall (104-146).

2 GROSS RENAL PATHOLOGY

With regard to the pathologic changes in the kidney, lupus nephritis was found in 28 percent (130) to 100 percent (193-246) of autopsy studies of pa-

tients dying of SLE Harvey and his colleagues (110) found some degree of renal involvement in 34 of the 38 patients with SLE on whom autopsies were made. In most large series of autopsy reports glomerular involvement was found in over 75 percent (9, 246, 269, 272). At autopsy the kidneys were usually somewhat larger than normal (12, 151). Their surfaces were smooth and in some cases were diffusely mottled with minute petechial hemorrhages (3, 151, 261). They resembled grossly the appearance of the kidney in acute diffuse glomerulonephritis or malignant nephrosclerosis (151). Contraction of the kidney is uncommon in lupus nephritis (193) but was noted in cases of SLE dying with chronic glomerulonephritis (193, 272, 277).

3 WIRE LOOP LESIONS FIBRINOID AND HYALINE THROMBI

In 23 patients with florid SLE on whom postmortem examinations were done Baehr, Klemperer and Schifrin (9) found renal involvement in eight. They found glomerulonephritis in two, glomerulitis in three and in thirteen they found that the glomerular loops were stiff and thick. These lesions were the most impressive microscopic abnormalities encountered in the kidney. Baehr and his colleagues coined the term wire loop to describe the lesions because the rigid walls of the glomerular capillaries resembled rather distinctly loops of bent wire. The lesions were characterized by a patchy bright eosinophilic thickening of one or more segments of the glomerular capillaries near the periphery of the glomerulus. With eosin stains the wire loop material resembled amyloid but did not stain with Congo red or take a metachromatic stain with crystal violet (151, 272). The wire loop material was shown to be fibrinoid in Neumann's sense (207). It stained red with Azan, deep mahogany brown with Bielschowsky silver stain (151) and red with the periodic acid Schiff reagent (183). When stained with Mallory Heidenhain stain the color varied from red to orange to blue and shades of purple were seen depending on the amount of fibrinoid swelling of the capillary tuft (3). The wire loop material did not give the collagen reaction with Van Gieson's or the Masson's trichrome stain (151).

The exact location of the fibrinoid wire loop material in the glomerular tufts has been a matter of controversy. It will probably remain an unsettled problem as long as the exact histology of the normal glomerular tuft is in doubt. Klemperer, Pollack and Baehr (151) dissolved wire loop material out of the glomerular tufts with trypsin and found an empty space between the endothelium and epithelium. Recently Churg and Grishman (51) have studied the locus of glomerular fibrinoid by phase microscopy and the Mallory Gallego stain. Their findings also indicate that wire loop material lies between the epithelial and endothelial basement membranes. Thus far electron microscopy (80) has not solved this problem. Although it has been emphasized that wire loop lesions were pathognomonic for SLE (9) Klemperer also observed wire loop lesions in five of 43 cases of subacute and chronic glomerulonephritis (151). In addition lesions resembling wire loops have also been observed in eclampsia (3, 232), scleroderma (3), dermatomyositis (3), malignant hypertension (3, 151) and renal vein thrombosis (231).

Another lesion observed in the kidney in SLE is the hyaline thrombus. Hyaline thrombi were found in a small percentage of those cases in which wire loop involvement of the kidney was demonstrated. They were seen within the capillary lumen and appeared to blend with the walls. They were refractile, homogeneous and eosinophilic and had the same appearance and staining qualities as wire loop material. Klemperer and his colleagues (151) originally believed hyaline thrombi to be an extreme development of the fibrinoid alteration of the capillary wall but Allen (3) considered them to be verrucal swellings of the glomerular capillary wall.

4 FOCAL NECROTIZING GLOMERULITIS AND ENDOTHELIAL CELL PROLIFERATION

Bizarre and pyknotic glomerular cell nuclei were noted in association with severe wire loop changes. In some areas of gross fibrinoid change obvious necrotic lesions were seen (151, 264). These changes in the glomerular tufts presented a pathologic picture termed focal necrotizing glomerulitis. These lesions resembled those seen in the focal embolic glomerulonephritis first described by Lohlein (11, 172) in patients who died of subacute bacterial endocarditis. Klemperer (151) believed that focal glomerular necrosis and the wire loop lesions were different grades of the same process. He related the development of the lesions to the intensity of the process and noted that focal necrosis of the capillary tufts might occur in the absence of wire loop change. However, Klemperer pointed out that the development in SLE of focal necrotizing glomerulitis was not related to the presence or absence of verrucous endocarditis of Libman Sacks.

Stickney (272, 274) studied the kidneys of 15 patients who died of SLE. He observed that the most common pathologic lesion in lupus nephritis was an increase in the number of endothelial cells in the glomerular capillaries. Proliferation of the e cells was found in seven of the fifteen cases. He also observed hyaline thickening of the capillary walls in five of the cases but noted the wire loop lesion in only one.

5 HEMATOXYLIN STAINED BODIES

Hematoxylin stained bodies were first observed in the heart valves and valve pockets in patients with atypical verrucous endocarditis (103). These smudgy, diffuse lavender staining, amorphous bodies have also been found in the kidneys of patients ill with SLE (149). They were seen lying free in the lumen of the glomerular capillaries (149) in the intertubular capillaries (104) and rarely within the substance of hyaline thrombi in the glomerular capillary lumen (51). They were easily distinguishable from pyknotic or lysed nuclei (karyorrhexis). Klemperer found hematoxylin bodies in the kidneys from 41 of 45 cases of SLE (146). He and his colleagues did not find hematoxylin bodies in acute or chronic diffuse glomerulonephritis, rheumatic or bacterial endocar-

them in patients with hyperglobulinemia (66). However most authors believe that hematoxylin bodies constitute a reliable criterion for the diagnosis of SLE in autopsy material (104-150).

The hematoxylin bodies were thought to be derived from the nuclei of fibroblasts, macrophages, lymphocytes and polymorphonuclear leucocytes (104). They were found to be Feulgen positive, methyl green negative and strongly absorbent in the ultraviolet spectrum at 237 Angstroms. When they were treated with trichloroacetic acid they were found to lose the ability to absorb ultraviolet rays of the same wave length and to become Feulgen negative (150). The above staining reactions suggested that hematoxylin bodies were composed of depolymerized deoxyribonucleic acid (150-233). Special studies have shown progressive degradation of the deoxyribose nucleic acid of the nucleoprotein and ultimate disappearance of the nucleic acid molecule (104). Morphologically (25) and histochemically (104-150) they were found to be similar to the smudgy purple glomerular hyaline thrombi (34) and to the phagocytized masses seen within the Hargraves cells (109-149-150).

6. SUBACUTE AND CHRONIC GLOMERULONEPHRITIS

Typical subacute glomerulonephritis with epithelial crescents has been observed in SLE by numerous investigators (63-151-167-272). Daugherty and Baggenstoss (63) associated the histologic evidence of typical glomerulonephritic renal lesions with the clinical development of the nephrotic syndrome in their patients with SLE. In this type of glomerulonephritis they found proliferation of the endothelial cells of the capillaries. In some instances they also noted fibrinoid necrosis of the basement membrane and wire loop changes.

7. INVOLVEMENT OF TUBULES, INTERSTITIUM AND VESSELS

Fatty degeneration of the tubular epithelium was seen in the kidneys of patients who had the nephrotic syndrome due to lupus nephritis. The fatty vacuolization was associated with changes in the glomeruli (35). In reviewing the literature we noted that interstitial edema was rarely mentioned. Focal interstitial infiltration with lymphocytes, plasma cells and histiocytes occurred frequently (151) but this finding carried no more significance than in general autopsy material. The renal arterioles were not infrequently involved and the lesions of SLE were reported to have been similar to those seen in malignant nephrosclerosis or polyarteritis nodosa (12). Pyelonephritis (180-277), renal abscesses (126-266), renal infarcts (272) and chronic arteriolo nephrosclerosis (245) have been described in association with SLE.

IV. REVIEW OF THE ETIOLOGY AND PATHOGENESIS OF THE RENAL LESIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS

The etiology of systemic lupus erythematosus remains undolved. Theories regarding the nature of SLE have followed fashionable trends in medical thought. In turn drathosis, tuberculoi, syphilis and other infectious diseases, focal infection, auto-intoxication from the putrid products of digestion and allergy

have been blamed. In recent years it has become popular to incriminate hyperimmune reactions to the streptococcus, dysfunctions of the pituitary-adrenal axis, and stressful life situations. More recently it was postulated that in patients ill with the collagen diseases, the proliferation of plasma cells in the tissues and the elevation of gamma globulin in the serum had pathogenetic significance. The effect of the elevated gamma globulin would be to produce systemic injury of the connective tissues. For this reason the collagen diseases have been classified as dysgammaglobulinemias (69).

Early observers suggested a variety of local and traumatic causes for the appearance of skin lesions in lupus erythematosus (143). French (53, 221), German and Viennese (70, 105, 157, 277) investigators supported the theory that lupus erythematosus was of tuberculous origin. Keil (136) in a comprehensive review of this subject showed that this view was untenable. He investigated the postmortem reports in the literature and determined that in only 20% was there any possibility of active tuberculosis, and in some of these cases the disease was probably inactive prior to the onset of SLE. Four years later he was the first to use the term systemic lupus erythematosus (137).

In 1919 Bari'er suggested that streptococcal infections might be the cause of lupus erythematosus (15, 16). Since then many cases have been reported in which streptococci seemed to play a prominent etiological role (173, 193, 203). Bulote considered it that the disease was due to an ultramicroscopic agent (20) and Moulton and Clark claimed to have isolated a virus from the blood of patients with SLE (194). This has not been confirmed by other investigators. Keith and Rowntree (141) emphasized the danger of removing or disturbing foci of infection if there were signs of activity in the disease. Although positive blood cultures have been obtained in the terminal stages of the disease (176)—especially when secondarily invading organisms may be expected to have been present—recent bacteriological studies have not supported the view that organisms cause SLE (101).

Crocker (61) suggested a possible endocrine etiology. The preponderance of SLE in women has been attributed to ovarian dysfunction and to pregnancy (157). From a questionnaire submitted to 100 dermatologists it was concluded that pregnancy had no significant effect on the clinical course of lupus erythematosus (73). Rose and Pillsbury (246, 247) observed a high incidence of acute disseminated lupus erythematosus in women during active menstrual life and emphasized the occurrence of premenstrual exacerbations of the disease. Castration (209) and testosterone therapy (11) have had no beneficial effects on SLE. Clinical and laboratory findings consistent with SLE were noted in 15 percent of 128 patients with rheumatoid arthritis and hypercorticism. Half of these patients had evidence of renal involvement as indicated by a blood urea level in excess of 40 mg/100 ml, cylindruria, persistent microscopic hematuria or albuminuria, or some combination of these findings (80).

Klinge (153) was among the first to suggest that allergic or hypersensitivity reactions played an important role in the etiology of a number of diseases characterized by fibrinoid degeneration of connective tissue. Fox (79) observed the

onset of SLE following administration of foreign protein Stokes, Berman and Ingraham (276) suggested that infectious allergic agents produced vascular allergic manifestations leading to lupus erythematosus. Since then many authors (108, 124, 239, 242, 286, 298) have stressed that an antigen antibody reaction may cause SLE and other collagen diseases or diseases of reaction. A possible relationship to the Schwartzman reaction has been suggested by the recent studies of Brunson and his colleagues (38, 39, 40) and of Booth, Muirhead and Montgomery (32). The widespread use of chemotherapeutic and antibiotic agents has been correlated with an apparent increase in the incidence of SLE and other collagen diseases—in particular, polyarteritis nodosa. For example Gold (96) stated that in approximately 87% of his patients sulfonamide or penicillin therapy preceded the onset of SLE. However, Baehr and Pollak (11) found no valid evidence to support this concept and concluded that the development of SLE was coincidental to chemotherapy or antibiotic therapy. Teilmann (284) suggested that the features of focal glomerulonephritis in SLE were analogous to other changes which could be interpreted as part of an allergic reaction—similar to the Arthus phenomenon. He suggested the possibility that the hypergammaglobulinemia of SLE may be the cause of the renal lesions. Teilmann also observed certain similarities between SLE and sarcoidosis (285, 286) and stressed the relationship between the two.

Recently Kurnick (159) has studied the mechanism of the Hargraves cell phenomenon. He concluded that an abnormal factor in the gamma globulin altered the cell membrane. This allowed a proteolytic enzyme in Fraction III of serum to enter the cell where it destroyed the protein inhibitor of deoxyribonuclease. The uninhibited deoxyribonuclease attacked chromosomal deoxyribonucleic acid which in turn changed into the depolymerized nuclear mass so characteristic of fibrinoid, hyaline thrombi and the Hargraves cell. Jindra, Solon (122, 123), Stickney (272, 274), Montgomery (190) and others (193) supported the view that some toxic irritating substance produced renal damage (81). No such substance has been isolated. Many other etiological factors have been implicated—these include nervous fatigue (74), the pleuropneumonia group of organisms (37), hereditary syphilis (221), lead intoxication (174), and a special affinity of the vascular system for the ferments of lymphocytes (87).

The reports (68, 119, 223, 238, 257) of a syndrome indistinguishable clinically from SLE occurring during the treatment of hypertensive patients with hydralazine are of some interest to those who believe that SLE is a disease of reaction involving ground substance and connective tissues. These reports strengthen the hand of those who believe that the upsurge in the diagnosis of SLE is the result of a reaction in certain sensitive individuals to antibiotics and can be related to the widespread use of these agents. The fact that the SLE like syndrome subsides completely when hydralazine therapy is stopped indicates that the reaction does not produce the disease *SLE de novo*. It may unmask subclinical SLE. It may provide a clue to the etiology of SLE but it is quite possible that it is producing a syndrome which we classify as SLE because of our imperfect knowledge of the clinical spectrum of the disease and even more

because of our profound ignorance of its cause. Nevertheless, Reinhardt and Waldron (238) found acute collagenous necrosis in the skin biopsy of one of these patients and Dammin *et al* (62) reported a case with LE cells ante mortem and postmortem in whom they found renal splenic and other lesions consistent with SLE.

Comens (57) has produced a syndrome resembling SLE by the administration of hydralazine to dogs. Hargraves cells were demonstrated in the peripheral blood of these animals. He concluded that pathologic specimens of the kidneys revealed changes consistent with those found in disseminated lupus erythematosus. Although fibrinoid degeneration was found in two specimens we cannot agree with this conclusion. The wire loop lesion demonstrated does not resemble that seen in biopsy or autopsy specimens from patients with SLE and the lesions more peculiar to lupus nephritis did not occur in the kidneys of these hydralazine treated dogs.

In recent years clinicians have become aware of a new organ system in the body—the ground substance (*substance fondamentale* or *grundsubstanz*) and its associated connective tissues. The development of new tests for the study of diseases involving the ground substance does not mean that we have the right to separate etiologically diseases of this organ on the basis of these tests. The presence of the Hargraves cell and its associated phenomena implies to many people a definitive diagnosis of lupus erythematosus but this may not be the case. We do not as yet recognize the limitations and usefulness of any single one of the many LE cell tests presently being used and it would be unwise—historically speaking and at the present time—to classify everyone with a positive LE cell test as having systemic lupus erythematosus (129). All of us who are old enough recognize that we treated many patients with positive Wassermann tests for syphilis despite their vehement denials that an opportunity had ever arisen for them to contract this venerable disease. We now recognize to our dismay that 30 years after Wassermann described his test we were treating unnecessarily patients who suffered with infectious mononucleosis, SLE and other diseases in which the Wassermann reaction was positive. Although new instruments and new tests may illuminate a disease process the physician produces iatrogenic diseases when he uses them to make injudicious deductions therefrom—deductions which are invalid because the test is not understood or because its limitations have not been worked out.

Unfortunately there is no such thing as a pathognomonic sign or test for any disease. There are always exceptions which prove the rule. Some now consider that dysgammaglobulinemia is the cause of diseases which affect the ground substance. Two hundred years ago it was popular to think of fevers as being the cause of a variety of infectious diseases. We now understand that fevers are the result and not the cause of infectious diseases and it may well be that dysgammaglobulinemias are the result and not the cause of diseases of the

ogy distinct from that of SLE need be invoked to explain lupus nephritis. Serial biopsy studies of the kidney provide a sure and simple method to clarify the histogenesis of the renal lesions. It is our hope that in the future the application of physical and chemical methods to renal biopsy specimens may further elucidate the reactions of the ground substance in this disease.

V METHODS OF STUDY

I SELECTION OF PATIENTS

Systemic lupus erythematosus presents itself in many a bizarre guise. Its course is variable and is usually characterized by acute or chronic episodic illness followed by partial or complete remissions. There are no clinical or laboratory findings peculiar only to this disease. In each patient the diagnosis was made on the basis of a broad spectrum of clinical and laboratory findings in which the clinical history was most important. Thirteen clinical and nine laboratory criteria were used to validate the selection of patients for this study. They are set forth in Tables I to III.

Thirty-three patients were carefully selected on the medical services of three hospitals (Table I). Fourteen Negroes and nineteen Whites were studied. At the time of their entry into the study, the ages of the 28 females varied from 11 to 61 years (average age 28.9 years), and the ages of the five males varied from 15 to 47 years (average age 32.2 years) (Fig. 1). Of the thirteen symptoms and signs considered by us to be important clinical characteristics of SLE, nine or more were found in 30 patients, and in no patient were fewer than seven noted (Table I and Fig. 2). At least five of the nine laboratory criteria were observed in 32 of the 33 patients (Tables II and III and Figure 3). Thirty-two patients had a face rash, and 31 suffered from involvement of their joints. Every patient had recurrent bouts of fever, and in all the clinical course was characterized by exacerbations and remissions. Evidence of involvement of the serous membranes, either of effusions into the serous cavities or of recurrent pleuritic and abdominal pain, was noted in all patients. Enlargement of the liver, spleen, or lymph nodes was found at some stage of the illness in every patient. Characteristically these were associated with exacerbations of the clinical illness, and the size of the affected organs returned towards normal as the clinical state of the patient improved.

The erythrocyte sedimentation rate (ESR) was invariably elevated. Anemia or leucopenia was observed in 28 patients. In 31, the serum globulin level was elevated, and in every patient the thymol turbidity test was positive. Hargraves cells were found on examination of the bone marrow or peripheral blood in 26 patients.

II THE STUDY OF RENAL FUNCTION

After the diagnosis of SLE had been made, the patients were studied in hospital and were followed in a special clinic. The function of the kidney was as

assed by the following tests

a Urinalysis In erythrocytally non-specific specimens of urine were examined solely after collection by one of us (RCM or VEP). Clean voided specimens from male patients and either specific specimens from female patients were examined. A portion of each specimen submitted for bacteriologic culture. Fluids were refrigerated for 12 hours before the collection of the specimen for urinalysis.

The specific gravity of the urine was tested at room temperature with a standard 1:1000 refractometer. The pO₂ was estimated semiquantitatively using the urofoscylic acid

pernate and heparinized sediment resuspended by agitating a few drops of urine. It was then examined microscopically with low and high power magnification. Polarized light was used for the identification of anisotropic lipids.

b Tests of Renal Function
) The specific gravity of the urine was measured following a period of 14 hours of fluid intake on 100 cc specimens of urine were collected and the maximum specific gravity was recorded.

Urea Clearance (188) were determined for a single two-hour period in a average urine flow of at least 2 ml per minute as attained in most patients. Test results were reported as a percentage of a normal male renal function (5 ml/min/100 cc when the urine flow is average 2 ml/min 54 ml/min 100 cc when the urine flow is 1.5 ml/min).

) PSP test on 6 mg of phenolsulfonphthalein (PSP) was measured intravenously after a water load had been given (240). The bladder was emptied completely 15 minutes later and the excretion of PSP as measured on a Coleman Junior spectrophotometer.

In a few instances measurements of effective renal plasma flow (ERPF) glomerular filtration (GFR) and tubular excretion of inulin (T_{in}) were made by using inulin and para-amino hippuric acid (PAH) according to the methods of Golding and Christ (98).

Biochemical Examination of the Blood In all cases the following biochemical examinations of the blood were done: blood cell count by the method of Fickers (94); blood urea nitrogen by the Conway method (58); blood non-protein nitrogen by the method described by Iolin and McMeekin (155); serum protein by the Coln method (121, 303); total serum calcium by the method described by a modification of the Borethol (90) titrimetric method according to the method described by Slink and Hoag (98). When indicated serum sodium and potassium were measured in serum and distillate plasma.

Serum calcium was measured by the method of Scales and Siles (254) and the CO₂ combining power by the method of Van Slyke and Neil (99). The serum cholesterol was 156 to 160 mg/ml in patients with nephrosis and pseudonephrotic syndrome.

3.1.1. HISTOLOGIC METHOD

A 5 ml sample of venous blood was obtained using a 25 ml syringe and oxalate or lithium oxalate anticoagulant. The serum was separated and 100 μl was placed in a test tube and the erythrocyte sedimentation rate was measured by the method of Westergren (304). Urine was examined in both chambers of an unmodified Neubauer hemacytometer. The sedimentation was measured by the modified method of Lee and White (220) and the sedimentation times by the method of Duke. The sedimentation rate was measured by the quantitative method (235). Direct and indirect Coombs tests were performed on all patients (59).

Examination of Haemolytic Cells Clotted blood or bone marrow was incubated for one half to two hours. The clots were broken up and the leucocytes were concentrated and examined on slides stained with Wright's stain. Test slides were examined for at least 5 minutes under

TABLE I

Clinical data on 53 patients till with systemic lupus erythematosus on whom renal biopsies were done

Case No.	Patient's Initials Sex Age (yrs)	Duration of Disease		Date of Biopsy	Pathologic Diagnosis ¹	Renal Clinical Course	Fever	Enlargement of			Serous			Arthritis or Aneurysms	Cholesterol			Myocarditis	Raynaud's Phenomenon	Remarks
		Pre study (yrs)	Post study (mos)					Lymph nodes	Liver	Spleen	Plena	Pericardium	Peritoneum		Face	Genitalia	Thighs and Joints			
1	N. F. 28	II	8	1/0 55	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Onset Acute hemolytic anemia
2	D. M. K. F. 29	15	3	6/18 55	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Myxedema Vague symptoms for 10 years
3	M. W. d. F. 31	5 1/2	12	9/3 54 1 25 55	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Sl. n. b. opay positive
4	E. D. F. 24	11	18	2/17 54 9 8 54	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Thrombocytopenic phenomenon for 8 years before other symptoms
5	P. H. F. 19	5 1/2	8	1/12 55 5/10 55	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
6	J. S. T. 24	13 1/2	14	7/14 54 11/21 54 5 27 55	N N N N N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Sl. n. b. opay positive Hypertension
7	M. T. F. 30	5	23	10 17 52 9 9 54 6 5 55	N N N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Sl. n. b. opay positive
8	M. W. r. F. 34	9 1/2	11	9/14 54 1/16 55	N N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Dead Acute exacerbation with thrombocytopenia and convulsions
9	J. A. M. 15	9	5	3/7 55	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Face rash for 9 years before other symptoms Two episodes of hemiplegia Thrombocytopenia

F's of renal biopsy normal

TAB I I—(continued)

Case Patient's Initials No. Sex Age (Yrs.)	Duration of Disease		Date of Biopsy	Pathologic Diagnosis	Renal Course	Fever	Enlargement of			Serositis			Skin Lesions			Myocarditis	Raynaud's Phenomenon	Remarks
	Pre-study (Yr.)	Post-study (mo.)					Lymph nodes	Liver	Spleen	Pleura	Pericardium	Peritoneum	Arthritis or Aneurysm	Face rash	Scaly rash			
<i>First biopsy membranous glomerulonephritis</i>																		
70 P M 35	9 1/2	8	1-3-55	MG (II)	+	+	+	+	+	+	+	+	+	+	+	+	+	0
81 D B 44	1 1/2	7	2/28-55 7-1-55	MG (I & II) MC (N O G)	+	+	+	+	+	+	+	+	+	+	+	+	+	0
<i>First biopsy membranous glomerulonephritis</i>																		
22 J M 47	11	9	2/28-55 6/18-55 11/15-55	GN (N O R) DR DN GN (N O R)	+	+	+	+	+	+	+	+	+	+	+	+	+	0
23 E R F 33	6	19	7/11/54 10-5-54 2/17/55 6/16-55 1-11/55	MG (N O R) SG (N O R) CC (N O R) CG (N O R) CC (N O R)A	+	+	+	+	+	+	+	+	+	+	+	+	+	0
21 W 11 M 46	1 1/2	3	6/7-55	MC (N O R)	+	+	+	+	+	+	+	+	+	+	+	+	+	0
25 R N F 50	1 1/2	12	5-76-54 5-9-55	MPC (N O R) MC (N O R)A	+	+	+	+	+	+	+	+	+	+	+	+	+	0
29 J M 27	2 1/2	2	10-17-53 1-12-55	MPC (N O R) CG (N O R)A	+	+	+	+	+	+	+	+	+	+	+	+	+	0
27 M 1 1 27	2 1/2	1	4/4-55 5/15-55	MIG (N O R) MIG (N O R)A	+	+	+	+	+	+	+	+	+	+	+	+	+	0

TABLE II
Urinary findings and tests of renal function in 55 patients with systemic lupus erythematosus

Case No.	Sex and Age (Yrs.)	Duration of Disease		Date of Biopsy	Pathologic Diagnosis	Proteinuria (Fas or gm/24 Hrs.)	Microscopic Urinary		Non Protein Nitrogen (mg/100 ml)	Urea Nitrogen (mg/100 ml)	Creatinine (mg/100 ml)	Sp Gr: Max Sp Gr	15 Min Fac % Total Dose	Urea Clearance Test (% ANRF)
		Pre study (Yrs.)	Post study (Yrs.)				RBC	WBC						
1 N K	M 23	2	8	1/20/55	N	0	0	0	28	8	0.9	1.021*	34	80
2 D MeK	F 20	15	3	6/18/55	N	+	6-8	0	Occasional	0	1.0	1.036*	29	56
3 M Wd	F 31	6 1/2	12	9/3/54	N	0	0	3-5	Occasional	0	1.1	1.028*	33	89
				1/3/55	N	0	0	5-8	WBC (few)	7	1.0	1.028*	27	103
4 P D	F 24	11	III	2/17/54	I	0.3	0	0	Occasional	0	1.1	1.038*	25	100
				8/8/54	N	0	7	7	Occasional	11	0.9	1.032*	22	118
5 P H	M 19	3 1/2	8	1/12/55	N	0.2	0	2	Occasional	8	1.1	1.028*	17	53
				5/19/55	N	0	0	4	Occasional	8	—	1.030*	41	—
6 T S	F 21	1 1/2	14	7/14/54	N	0	0	0	Occasional	23	1.0	1.032*	29	91
				11/24/54	MC N (I)	+	0	15	Many granular casts on 1 cellular	36	1.0	1.020*	21	82
				5/27/55	MC N (II)	0	10-12	3	Occasional	32	1.0	1.024*	17	90
7 M T	F 39	3	23	10/19/55	N	0	0	0	Occasional	27	0.8	1.034	60	72
				6/8/54	III	0	0	0	Occasional	29	1.1	1.022	25	78
				4/5/55	III	0.4	3	3	Occasional	17	0.9	1.030	34	—
8 M W r	M 24	5 1/2	11	9/11/54	N	0	0	0	Occasional	32	1.0	1.034	34	76
				1/16/55	III	0	0	2.5	Occasional	24	1.2	1.024*	III	112
				6/21/55	III	+++	15-20	2.2	Occasional	—	1.1	1.020	III	—
9 J A	M 15	9	5	3/21/55	N	0	0	0	Occasional	27	1.0	1.025	32	115
10 M S	M 64	25 1/2	15	4/19/54	III	0.6	0	7	Crystalline	39	0.9	1.030	7	53
				6/17/55	I	+	0	7	Crystalline	27	1.3	1.016*	14	35
11 J D	F 13	5 1/2	14	5/8/54	N	0.5	0	0	Occasional	27	0.8	1.020*	III	76
				11/21/57	N	1.2	0	5-8	Occasional	III	1.0	1.020*	III	150
				7/2/55	MC N (I) (II)	+	0	0	Occasional	38	—	1.015	—	—

First renal biopsy normal

TABII II—Continued

Case No.	Patients in family	Sex and Age (Yrs.)	Duration of Disease		Date of Birth	Pathologic Diagnosis	Proteinuria Plus Urates or Grams/24 Hrs.	RBC	WBC	Mammographic Ur analysis		Non-Protein Nitrogen (mg/100 ml)	Urea Nitrogen (mg/100 ml)	Creatinine (mg/100 ml)	Sp. Gr. of Urine	Sp. Gr. of Urine (one Test)	Sp. Gr. of Urine (Max)	Sp. Gr. of Urine (Min)	15 Min. Post-Prandial Urine (Total Volume)	Urea Clearance (ml/min/1.73 m ²)
			Prevalence (yrs.)	Post-study (mos)						Casts	Casts									
23	18	T 33	6	18	7/11/51	MCN (I, R)	9	40-50	3-5	Many 1-3 granular fatty	15	28	2.5	1.018*	1.018*	1.018*	1.018*	6	11	
					10/5/51	MCN (I, R)	23	40-50	5-10	Many 1-3 granular fatty	47	27	3.3	1.018*	1.018*	1.018*	1.018*	5.5	13	
					2/17/53	CCN (I, R)	7.6	25-50	2-5	Many 1-3 granular	47	17	4.7	1.018*	1.018*	1.018*	1.018*	4	4	
					9/10/55	CCN (I, R)	++++	Macro	3-4	Many 1-3 granular	61	59	7.9	1.018*	1.018*	1.018*	1.018*	0	9	
					3/11/59	CCN (I, R)	++++	Many	Many	Many 1-3 granular	114	74	19.6	1.010	1.010	1.010	1.010	—	35	
21	11	M 46	1 1/2	3	6/7/53	MCN (I, R)	9.2	4	5	Hyaline granular	41	18	2.0	1.018*	1.018*	1.018*	1.018*	16	—	
22	11	F 29	1 1/2	17	5/26/54	MCN (I, R)	3.6	0	5-10	Crystalline	36	15	3.3	1.028	1.028	1.028	1.028	18	18	
					5/9/55	MCN (I, R)	3.9	10-50	5-10	Hyaline granular	150	—	—	1.00	1.00	1.00	1.00	18	48	
25	11	M 33	2 1/2	3	10/17/51	MCN (I, R)	++	3	15	Crystalline	25	18	0.8	1.020*	1.020*	1.020*	1.020*	28	29	
					12/12/55	MCN (I, R)	++++	3	15	Crystalline	40	—	—	1.014	1.014	1.014	1.014	—	—	
27	11	F 27	3 1/2	1	1/4/55	MCN (I, R)	++++	—	35	Hyaline granular	200	—	—	1.010	1.010	1.010	1.010	—	—	
					5/19/55	MCN (I, R)	++++	—	—	—	—	—	—	—	—	—	—	—	—	
28	11	F 60	0	0	11/21/53	MCN (I, R)	++++	15-50	5-8	Crystalline	43	24	0.9	1.02	1.02	1.02	1.02	15	18	

P. at 6 post study check on c-glomerulonephritis

29	11	R 6	15	6/7/51	CCN (I, R)	++++	5-50	0	0	Hyaline granular	60	37	1.6	1.018*	1.018*	1.018*	1.018*	18	16
					9/27/51	CCN (I, R)	+++	2-5	5-8	Hyaline granular	111	46	1.7	1.018*	1.018*	1.018*	1.018*	17	27
					6/21/55	CCN (I, R)	2.7	3-5	0	Hyaline granular	51	31	1.7	1.018*	1.018*	1.018*	1.018*	18	42
30	11	R 8	1 1/2	9/5	1/18/53	CCN (I, R)	1.2	40-50	40-50	Many hyaline granular	47	34	3.1	1.010*	1.010*	1.010*	1.010*	0	—
					3/30/56	CCN (I, R)	+++	Many	Many	Many	21	—	—	1.007	1.007	1.007	1.007	—	—
31	11	M 21	2 1/2	2 1/2	9/18/53	CCN (I, R)	2.4	10-20	5-10	Hyaline granular	66	44	3.2	1.020*	1.020*	1.020*	1.020*	13	37
					1/25/54	CCN (I, R)	10	10-35	10-15	Crystalline	101	—	—	1.013*	1.013*	1.013*	1.013*	7	13
					8/17/55	CCN (I, R)	++++	40-50	5-8	Crystalline	216	—	—	23.5	23.5	23.5	23.5	—	—

TABLE III
 Other pertinent laboratory data on 33 patients with systemic lupus erythematosus on whom renal biopsies were done

Case No.	Patents in tails	Sex and Age (Yrs)	Duration of Disease		Date of Biopsy	Pathologic Diagnosis*	Serum Cholesterol (mg/100 ml)	Serum Albumin (gm/100 ml)	Serum Globulin (gm/100 ml)	Serum Cholinesterase activity units/hour	Thymol Turbidity Test	Coombs Test		Wassermann Test	Hemoglobin (g%)	WBC (/mm ³)	ESR (mm/hour)
			Pre-study (Yrs)	Post-study (mos)								Direct	Indirect				
1	Nh	F 23	2	0	1/20 55	N	25	8.2	2.8	—	12.7	+	0	0	42	3500	11
2	D Vch	F 29	7.5	0	6/18 55	N	470	4.9	2.0	0.62	8.6	0	0	0	34	4400	27
3	M Wd	F 31	6 1/2	12	9/3/54 1/25 55	N	332 308	5.2 5.1	2.1 3.1	— 0.97	4.7 7.7	0	0	0	33	6000	23
4	D D	F 34	11	18	2/37 54 9 8 54	I N	179 159	4.6 4.6	2.9 3.2	—	7.0	+	+	0	41 37	4000	35
5	F H	F 19	2 1/2	8	1/12 55 5 19 55	N N	227 340	3.6 4.3	2.7 3.8	0.51	8.8 4.4	+	0	0	40 40	8600 8900	24 34
6	J B	F 24	1 1/2	14	7/14 55 11/24 55 5 27 55	N MG N (O) MG N (O)	— 372 332	2.6 4.1 4.7	2.5 2.6 3.2	—	3.1 14.5 11.0	+	0	0	30 42 41	8100 6100 9000	34 34 18
7	M T	F 30	3	23	10 17 55 8/9 54 8 5 55	N N N	246 258 550	4.4 4.5 3.8	2.9 2.3 2.0	—	12.0 13.8	0	0	0	33 41 40	8350 7000 900	24 31 46
8	M W	F 34	6 1/2	11	9/18 54 1/16 55 6/21/55D	N N —	246 350 —	2.9 2.5 4.4	3.4 3.9 4.8	0.60	27.8	0	0	0	32 42 25	12400 74300 20000	43 33 56
9	J A	M 18	9	5	3 21 55	N	240	5.0	3.7	—	23	0	0	0	49	8000	39
10	M S	F 61	2 1/2	13	5/18 54 6 17 55	no I	290 208	2.2 2.4	2.3 2.4	—	12.7 9.8	0	0	0	33 41	6000 5200	33 45
11	L D	F 15	6 1/2	14	5 18 54 11/24 54 7/12 55A	N N MG N (O, P)	200 156	2.9 3.7	4.0 4.2	—	13.2 12.7	+	0	0	33 31	3200	34

*First renal biopsy normal

F a b pay p olfira o maru =

2	II K	F 30	1 2	III	2 28 54 9 28 54 5 28 55	PMG I PMG I MPC I	2 5 227 21	4 8 4 7 5 1	3 6 3 0 3 2	18 5 10 3 18 7	0	0	+	+	26 42 40	7000 7000 6300	III III 28
3	M W	T 2	2	22	9 29 53 2 1 54 8 10 51 5 26 55	PA C (I E) PMG I E PMG N I E PMG N I E	220 3 0 262 3 0	3 8 3 1 3 2 4 1	4 3 3 3 4 3 3 8	22 3 7	+	0	+	34 36 32 41	17500	76	
14	M M	T 17		11	0 15 54 31 55	P I G E I M (E	220 3 5	3 9 3 3	4 8 4 0	22 5 0 47	0	0	+	3 32	8500	37	

F b b pay m m b anosa p one u o

5	M V P	F 4	1	5	5 7 54 4 9 55	I MG (I E	78 185	6 3 7	3 0 3 0	13 4 11 0	0	0	+	+	3 36	4700 5200	5
6	OK	M 32	1 2	5	6 12 54 6 17 55	MC (I E MG (I E	3 0 3 2	5 7 6 1	2 8 3 5	9 7 5 7	0	0	+	45 60	0	12 11	
17	P W	F 49	1 2	2	5 20 55	MG (I E	3 7	5 1	2 7	8 9	4 6	0	0	0	11	9400	26
8	M D	F 31	1/12	8	1 11 55 5 11 55	MG I E MG N E	29 746	4 0 3 5	4 3 4 4	6 70 4	0	0	84 Kaha u 12 Kaha	+	35 42	4100 4400	42 43
18	B J	F 11	1/4	14	6 18 54 2 10 55	MPC E MPC N E	246 425	3 8 2 2	4 4 5 7	16 0 62	+	+	+	31 30	3 00 8500	III	
III	P M	T 34	1/12	8	1 3 55	MG (181	3 0	4 3	9 4	0	0	+	35	6000	III	
21	D B	F 44	2	7	2 26 55 7 1 55	MPG (E MG N E	III III	2 8 7 9	3 6 5 0	III	0	0	+	34 6 38	4000	49	

F a b pay m m b anosa p one u on p b a

22	J M	M 47	11	9	2 28 55 6 6 55 11 4 55	MG N I E MC N I E GN O E	254 281 270	3 2 2 9	3 9 3 8	0 2 16 4 7 7	0	0	+	III 37 34	5400 4400 2700	54 III 30
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LUPUS NEPHRITIS

Case No.	Patients Initials	Sex and Age (Yrs)	Duration of Disease		Date of Biopsy	Pathologic Diagnosis*	Serum Cholesterol (mg/100 ml)	Serum Albumin (gm/100 ml)	Serum Globulin (gm/100 ml)	Serum Cholin esterase (Spft units/hour)	Thymol Turbidity Test	Coombs Test		Wasser man Test	Hem. (per cent)	WBC (/mm ³)	ESR (mm/hour)
			Pre study (yrs)	Post study (mos)								D rect	Ind rect				

Furth & opsy memb amous glomerulonephritis

23	F S	F 33	8	18	7/11/51 10/5/51 2/17/52	MC N (I g) SC N (I g) CC N (I g)	475 400 3.6	2.7 1.7 3.6	2.2 1.7 0.83	0.99 0.75 0.83	4	+	0	0	0	4000 7100 800	54 0 29
24	W H	M 45	1 1/2	3	6/7/55	MG N (I g)	480	2.6	3.6	0.92	4.3	0	0	0	100	2800	81
2a	R N	F 29	1 1/2	12	5/20/54 5/9/55A	MPC N (I g) MG N (I g)	212 410	3.5 3.4	2.7 3.9		12.9 12.3	0	0	0	44 31	10.50 14000	30 3*
2b	F V	F 27	2 1/2	2	10/17/53 12/12/53A	MG N (I g) RG N (I g)	215	3.0 2.5	4.1 3.9		19.7	0	+	0	35	4500	42
27	M T	M 27	1 1/2	1	8/4/55 5/10/55A	MPC N (I g) MPC N (I g)	-- 379	2.0	3.7	--	11.2	0	0	0	97	4100	4*
28	A W	M 26	6	6	11/9/54A	MPC N (I g)	165	2.6	3.1		8.0	0	0	+	93	4750	111

Furth & opsy subacute or chronic glomerulonephritis

28	R C	M 34	6	18	6/7/51 9/27/54 6/21/55	RC N (I g) CG N (I g) CC N (I g)	420 206 200	2.9 2.1 2.9	1.3 2.9 2.3		11.2	0	0	0	38 34 37	3010 4500 5100	42
30	B G	F 27	9 1/2	3	1/18/55 2/10/55A	SG N (I g) SC N (I g)	136	1.7 2.0	3.2 2.1	0.35	9.2	0	0	+	41 24	6500 13700	42 96
31	R /	M 31	2 1/2	2 1/2	9/18/53 4/27/54 8/12/55A	SG N (I g) CG N (I g) CG N (I g)	460 341 422	2.4 3.1 4.8	2.0 1.8 1.8		13 1 4.4	0	0	0	34 25 28	3900 5000 5000	35 7 7
32	B D	F 18	3 1/2	0	11/15/54A	SG N (I g)	322	2.2	3.2		12	0	0	0	21	2500	20
33	D J	M 15	2	2	7/18/55	CC N (I g)	173	2.9	3.5		8.6	0	0	0	111	900	30

* N renal I-100 mg Me PG-Ir I ferat ve gl merul sa MC-3000 mg mers 100 I G N I red ferat ve glomerul nepl rta MC N-Merul rnsia gl. or lncpl rta SC N-h tye to glomer lncpl rta CC N C I n n k mer lncpl rta (f)-Total (f)-Local (f) Diff ac (g) (e) renal and Nod. nucleolus A-Aut 100 B-D and No autopsy

the low power objective and suspicious cells were examined under the high dry objective. A preparation was not called positive if only one or two abnormal cells were found.

The Hargraves cell was defined as a polymorphonuclear neutrophil with one or more large inclusion bodies crowding the lobes to the edge of the cell. The typical inclusion body was as large as a normal neutrophil. It was homogenous unstructured without a sharply defined border and stained a reddish-violet to purple color with Wright's stain. We did not consider related phenomena adequate for diagnosis although they may have been suggestive. These phenomena were: free bodies of the same type as the inclusion material, some types of bodies surrounded by several neutrophils, smaller inclusion bodies in neutrophils, inclusion bodies in leucocytes other than neutrophils, inclusion bodies appearing to be within a vacuole or showing lobulation or creasing.

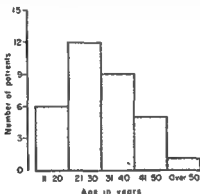


FIG 1 Age distribution of 33 patients ill with SLE studied by renal biopsy

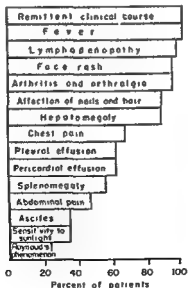


FIG 2 Percent incidence of symptoms and signs in 33 patients ill with SLE and studied by renal biopsy

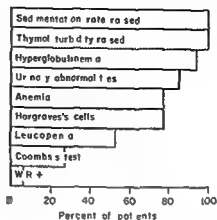


FIG. 3 Percent incidence of abnormal laboratory tests in 33 patients ill with SLE who were studied by renal biopsy.

4 RENAL BIOPSY AND RENAL PATHOLOGY

After the preliminary studies had been made a renal biopsy was done using the technique previously described. The cylinder of renal tissue was fixed immediately in 10% neutral formalin in saline. After fixation the specimen was embedded in paraffin and sections were cut at five microns. In all cases sections were stained with hematoxylin and eosin (H&E), with Mallory aniline blue (177) and with the periodic acid Schiff reagent (168). A minimum of five H&E sections and one each of Mallory aniline blue and PAS was studied in each case. In some cases frozen sections were stained with Oil red O for lipids (168) and in others paraffin sections were stained by the short Foot method for reticulum (168). In a few cases a portion of kidney tissue was fixed by the freezing drying method of Gersh (88) and stained for alkaline phosphatase by the Gomori technique (168).

The criteria commonly in use in pathologic studies were applied to the evaluation of the histologic lesions observed in biopsy and autopsy material. The relatively limited amount of material available for study presented new problems which have been discussed in previous papers (133, 135, 200). Only those biopsies which included adequate amounts of renal tissue were analyzed. The tissue was considered to be 'adequate' when five or more glomeruli and their adjacent tubules were present in the sections; in fact most of the biopsies contained ten or more glomeruli.

VI RESULTS

1 CLINICAL MATERIAL

Data on 33 selected patients ill with SLE have been summarized in the tables and charts. In general the patients have been classified in the tables on the basis of the renal pathology as this provides the most objective basis for study. However it has been impossible to divorce entirely the clinical from the patho-

logic features, and for this reason the data will be discussed on a clinicopathologic basis.

The criteria for selection of patients for study have been outlined in the section on method. The criteria used for selection and an analysis of the signs, symptoms, and laboratory investigations are set forth in Figures 2 and 3 and in Tables I to IV which also give details of the clinical features, urinary findings, tests of renal function, and laboratory and pathologic data of all patients. Definitions of the pathologic terms used are given at the beginning of section VI(2) (page 67).

One-third of the patients were found to have normal kidneys or minimal renal change when first studied, although they had systemic manifestations of the disease. This group of 11 patients provides controls in the study, and it is obvious that some time must elapse before we will have an opportunity to report on the development of their disease. Already in this group are 2 patients (#6, #11) whose renal disease has progressed—in one case considerably.

A Patients with normal renal biopsies

Eleven patients (cases #1-11) have been classified as having normal kidneys—so far as Lupus Nephritis is concerned—at the time of the first biopsy. One of these patients, a 61 year old lady (#10) had benign nephrosclerosis, but no other lesion in the kidney. Another (#3) had had several attacks of acute pyelonephritis. Abnormalities were found in the urine of both these patients. In three patients the renal biopsies were unquestionably normal, and in five (including #3) minimal changes were detected (See Section VI(2)—Pathology). These were so mild, however, that the kidneys have been classified as being normal. In three of the patients with essentially normal kidneys slight changes were found in the urinary sediment—usually a few erythrocytes or an excess of leucocytes. These findings were usually transient. The history of the following case illustrates this point.

Case 1

ED (R & L #6712) an intelligent 26 year old housewife had had multiple joint pains and Raynaud's phenomenon since 1944. In July 1952 she developed severe swelling of the feet following exposure to the sun. In August 1953 her joints became swollen. She had a fever, lost her appetite and was short of breath. The lymph nodes were enlarged. The liver and spleen were not enlarged. She had a pericardial effusion. The direct and indirect Coombs tests were positive and the serum globulin was elevated. Hargraves cells were found in the bone marrow. After treatment with ACTH was started her clinical condition improved. She was discharged from hospital and maintained in health with cortisone. Before treatment 3+ protein, leucocytes and casts were found in the urine. After her temperature was normal and no abnormality was found in the urine.

Episodes of arthralgia, pleuritic pain and low grade fever occurred. In February 1954 the skin of the forearms and fingers was red tense and appeared atrophic. There was a diffuse alopecia of the scalp. The lymph nodes were again enlarged. A renal biopsy was done on February 17. A few leucocytes were found in the urine. The GFR (C_{INULIN}) was 114 ml/min and the RPF (C_{PAH}) was 533 ml/min. A month later she developed gastroenteritis due to *Silmonella panama* but made an uneventful recovery after treatment with chloramphenicol.

TABLE IV—Continued

Case Patients No Initials	Pathologic Diagnosis*	Glomeruli										Tubules						Interstitialium			Vessels								
		Basic mem mem lysane	Cells fatty	Ischemia	Hyaline thrombi	Wire loop lesions	Karyorrhexis	Hematoxylin bodies	Fibrin mold	Embolic lesions	Adhesions	Crescents	Glomerular damage	Basement membrane	Degeneration	Atrophy	Dilatation	Protein	Casts	Tubular lamellae	Edema	Fibrosis	Inflammation	Sclerosis	Filmoid				
<i>First biopsy membranous glomerulonephritis—Continued</i>																													
23	EB MGN (G) SGN (I) CGN (G) CGN (G) CGN (G)	+++ +++ +++ +++ +++	0 ++ ++ ++ +	++ +++ +++ +++ +++	0 0 0 0 0	++ ++ ++ ++ ++	0 0 0 0 0	++ ++ ++ ++ ++	0 0 0 0 0	0 + + + ++	0 0 0 0 0	+++ +++ +++ +++ +++	++ +++ +++ +++ +++	++ +++ +++ +++ +++	++ +++ +++ +++ +++	++ +++ +++ +++ +++	++ +++ +++ +++ +++	++ +++ +++ +++ +++	++ +++ +++ +++ +++	++ +++ +++ +++ +++	++ +++ +++ +++ +++	++ +++ +++ +++ +++	++ +++ +++ +++ +++	++ +++ +++ +++ +++	++ +++ +++ +++ +++	++ +++ +++ +++ +++	++ +++ +++ +++ +++		
24	WY	+++	+	+++	0	++	0	++	0	0	+++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++		
25	RN	+++	+	+++	0	+	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++		
26	FL	+++	+++	+++	0	++	0	++	0	0	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++		
27	WJ	+++	+	+++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++		
28	AW	+++	++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++		
<i>First biopsy sclerotic or chronic glomerulonephritis</i>																													
29	RC	+++ +++ +++	++ + ±	+++ +++ +++	0 0 0	++ ++ ++	++ 0 0	++ 0 0	± ++ ++	0 0 0	0 0 0	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	
30	DS	+++	+++	+++	0	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++		
31	RE	+++ +++ +++	+++ +++ +++	+++ +++ +++	0 0 0	++ ++ ++	++ ++ ++	++ ++ ++	++ ++ ++	++ ++ ++	++ ++ ++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++	+++ +++ +++

In June 1954 she had a thrombophlebitis of the left leg. Three months later she was readmitted to hospital for study. A butterfly face rash was noted. The lymph nodes were enlarged and there was scleroderma-like. There was no peripheral edema and the blood pressure was normal. A renal biopsy was done on September 8. A few erythrocytes, leucocytes and cellular casts were found in the urine. Since that time she has been kept relatively free of symptoms with small doses of cortisone. Examination of the urine has been normal.

First Biopsy The first biopsy contained normal renal medulla but was inadequate for diagnosis.

Second Biopsy (September 1954) Adequate renal cortex (12 glomeruli) and medulla were included in the sections. The glomeruli were essentially normal. Bowman's spaces contained a moderate amount of proteinaceous material. The convoluted tubules also contained proteinaceous material and were lined by a slightly swollen and degenerated epithelium. The interstitial fibrous connective tissue and the small arteries were normal. A very small amount of intratubular material was seen in the cells of the convoluted tubules in sections stained with Oil Red-O. Gomori preparations for alkaline phosphatase disclosed the presence of abundant enzymatic activity in the cells of the convoluted tubules.

Diagnosis Essentially normal renal tissue.

The renal histology from two of the patients (Nos. 6, 11) was normal at the time of the first biopsy and urinalysis and renal function were not disturbed. Lupus nephritis developed and was found 10 months and 14 months after the first study. One patient died as a result of poliomyelitis, and the other is alive and reasonably well. The histories of these two patients are given below.

CASE 6

J.S. (R & E 417655) a nervous apprehensive 24 year old housewife had had rheumatic fever in childhood. She enjoyed good health until June 1953 when she developed an erythematous rash involving the face and upper chest following exposure to sunlight. She became acutely ill. A skin biopsy was done. Its histologic appearance was consistent with lupus erythematosus. In May 1954 she was short of breath on exertion and developed Raynaud's phenomenon. One month later she had migratory joint pains and was admitted to hospital. She was febrile, acutely ill, anemic and had a butterfly face rash and alopecia of the scalp. There was tachycardia, electrocardiographic evidence of myocarditis and a pericardial friction rub. The blood pressure was 140/60 mm Hg. There was a pleural effusion and a pleural friction rub was heard. The thyroid gland was diffusely enlarged and a bruit was heard over it. All lymph nodes were enlarged. Urinalysis and tests of renal function were normal. Many Hargraves cells were found on examination of the bone marrow. SLE and hyperthyroidism were diagnosed. The BMR and I¹³¹I uptake confirmed the latter diagnosis. She was treated with ACTH and methimazole and her condition improved dramatically. A renal biopsy was done on July 14. She gained 24 pounds in weight and when discharged from hospital she was free of symptoms and was being treated with small doses of cortisone.

In November 1954 she was readmitted for study. A faint face rash was seen. The skin over the fingers was thickened but the lymph nodes, liver and spleen were not enlarged. There was a trace of protein, many leucocytes and many granular and leucocyte casts in the urine. Renal function was slightly impaired. A second renal biopsy was done.

In January 1955 methimazole was discontinued but she continued to take cortisone. Four months later she was again studied in the hospital. There were areas of atrophic skin on the face. The skin of the forearm and fingers was tense and atrophic. The blood pressure

glomeruli) were included in the sections. Sixty-four questionnaires concerning the

membrane the glomeruli appeared essentially normal. There was a minimal increase in cellularity of the glomerular tufts and Bowman's spaces contained some proteinaceous material. The convoluted tubules were normal in size. The lining epithelium was somewhat swollen and their lumina contained a moderate amount of proteinaceous material. The interstitial tissue was not remarkable. Minimal thickening was seen in the walls of the small arteries.

Diagnosis: Essentially normal renal tissue. Questionable localized glomerulitis was seen.

Second Biopsy (November 1954) Adequate renal cortex (8 glomeruli) but no medulla was included in the sections. The glomeruli were slightly ischemic. Minimal local hypercellularity was noted and there was moderate local thickening of the basement membrane in several glomeruli. Bowman's spaces contained a moderate amount of proteinaceous material. The convoluted tubules were normal in size and were lined by a slightly degenerated epithelium. In several areas the tubules were atrophic. Their lumina contained a moderate amount of proteinaceous material. There was a slight increase of interstitial tissue and foci of chronic inflammatory cells were seen. Mild thickening and sclerosis was seen in the walls of the small arteries. Mallory and PAS preparations confirmed the above findings.

Diagnosis: Mild local and focal membranous glomerulonephritis.

Third Biopsy (May 1955) Small fragments of renal cortex (4 glomeruli) and medulla were included in the sections. The glomeruli were slightly ischemic and a slight but distinct local thickening of their basement membrane was noted. There was no definite hypercellularity and Bowman's spaces contained no proteinaceous material. Minimal degenerative changes were seen in the lining epithelium of the convoluted tubules which contained a small amount of proteinaceous material. Mild thickening and fibrosis were seen in the walls of the small arteries.

Diagnosis: Mild local and focal membranous glomerulonephritis.

Case 11

L.D. (R & E 4142-11) a 13 year old negro high school student enjoyed good health until January 1954 when she developed migratory arthritis of the ankles and knees. One month later she had anorexia, was coughing, was short of breath and had lost 16 pounds in weight. A diagnosis of tuberculosis was made and streptomycin and isoniazid prescribed. In March she was feverish and a butterfly rash appeared across the face. A diagnosis of erythema was made by a physician.

On admission to the University of Illinois Hospitals in March 1954 she was anemic, febrile, lethargic, acutely ill and complained of pain in the abdomen. The blood pressure was 80/0. There was tachycardia, a protodiastolic gallop rhythm and electrocardiographic evidence of myocarditis. There was an erythematous rash over the face, ears and distal phalanges. The conjunctivae were injected and the gums bled easily. The cervical lymph nodes and liver were enlarged. There were pericardial and pleural effusions. There was a trace of protein and several leucocytes, erythrocytes and hyaline casts in the urine. Many Hargraves cells were found on examination of the bone marrow. She was treated with ACTH and a remarkable clinical improvement took place. She became afebrile, the pleural and pericardial effusions decreased, the gallop rhythm disappeared and the PCC returned to normal. Urinalysis and hematocrit became normal. A renal biopsy was done on May 8. The GFR (C_{INDULIN}) was 117 ml/min and the RPF (C_{PAB}) was 668 ml/min and the T_{MPAH} was 76 mg/min. She was discharged from hospital on maintenance doses of cortisone.

In September she had a cough, mild dyspnea, pleuritic pain and a sore throat. Tender cystic nodules appeared on the dorsal surface of the interphalangeal joints. There were pericardial and pleural effusions. There was marked improvement of symptoms when the dosage of cortisone was increased. Except for mild dyspnea and pericardial pain she was

free of symptoms when admitted for study in October, 1951. Save for a butterfly face rash, slight alopecia of the scalp and cervical lymphadenopathy, the physical examination was normal. The direct Coombs test was positive. A second renal biopsy was done when the urinalysis, NPN, and tests of renal function were normal.

In June, 1955, she became lethargic, complained of headache and developed fever, a stiff neck, and a flaccid paralysis of her legs. On admission to the hospital her neck was stiff. There was weakness of arms and legs and the knee and ankle jerks were absent. The CSF pressure was increased, the protein was elevated, and 225 leucocytes (80% polymorphonuclears) were found in the spinal fluid. Poliomyelitis was diagnosed. She developed a severe, bilateral pneumonia, became comatose, and died seven days after admission. Post mortem examination confirmed the diagnosis of poliomyelitis.

First Biopsy (May 1954) Adequate renal cortex (6 glomeruli) but no medulla were included in the sections. The glomeruli were essentially normal except for slight ischemia and questionable local thickening of their basement membrane. There was slight degeneration of the lining epithelium of the convoluted tubules whose lumina contained proteinaceous material. The interstitial tissue and small arteries were normal.

Diagnosis: Essentially normal renal tissue

Second Biopsy (November 1954) (Fig. 4) Adequate renal cortex (8 glomeruli) and medulla were included in the sections. There was local thickening of the basement membrane. The mesangial spaces did not contain any cells. The tubules were dilated. They were lined by low cuboidal epithelium in which minimal degenerative changes

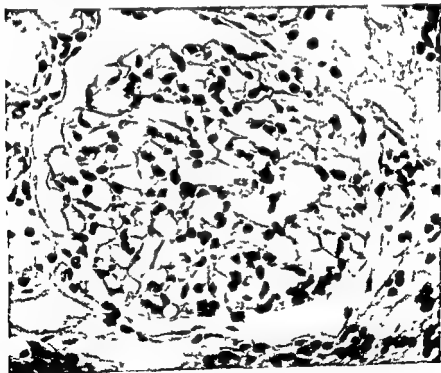


FIG. 4. Patient #11. Second Biopsy, October 1954. The glomerulus is essentially normal. The patient has been ill with SLL for nine months. (H&E $\times 620$)



FIG 5 Patient #11 Autopsy June 1958 Note the marked and rather diffuse smudgy thickening of the glomerular basement membrane—suggestive of fibrinoid The tubular epithelium is somewhat degenerated (H&E $\times 400$)

were noted The tubular lumina contained a small amount of proteinaceous material The interstitial tissue was normal Comparison with the previous biopsy disclosed no changes of note

Diagnosis Essentially normal renal tissue

Autopsy Specimen (July 1958) (Fig 5) The glomeruli were slightly lobulated and a distinct but mild to moderate local thickening was seen in the basement membrane Minimal local hypercellularity was also noted in the glomerular tufts In places the thickened glomerular basement membrane was smudgy in character suggestive of fibrinoid changes A few wire loop lesions were noted Hematoxylin bodies were not seen Brownish areas contained little or no proteinaceous material Moderate degeneration of the lining epithelium of the convoluted tubules was noted They contained proteinaceous material The capillaries and small veins were congested The interstitial tissue contained foci of chronic inflammatory cells especially numerous around some of the glomeruli and a few small arteries Mallory and PAS preparations confirmed these findings No lipid was seen within the epithelium of the convoluted tubules with Oil Red O preparations of frozen sections Comparison with the previous biopsies indicated a definite increase in the severity of the glomerular changes and in addition the presence of fibrinoid degeneration

Diagnosis Local and generalized membranous glomerulonephritis

B Patients with abnormal renal biopsies

When the first biopsies were made, the histology of the kidneys was abnormal in 22 cases At that time the urine of all but three of these patients (#12, 16, 19) was abnormal In general, renal function was not affected until the degree of

kidney damage was severe. In some of these patients the renal lesions and clinical status have changed little during the period of study. In others the renal lesions have progressed and the clinical status has deteriorated. Of the ten patients who died, six died of renal disease (§23, 25, 26, 30, 31, 32), one of renal disease and acute pancreatitis (§27), one during an acute exacerbation of SLE with myocarditis and severe renal damage (§28). One patient died of anterior poliomyelitis (§11). Her kidneys, which had been normal when first studied were the seat of moderate membranous glomerulonephritis at the time of her death. The tenth (§8) died of an acute exacerbation of SLE, terminally there were abnormalities in the urine, but the last histologic study, made seven months previously, was normal.

The clinicopathologic features of the patients whose kidneys were abnormal will be discussed below under the following headings:

- (1) Mild Lupus Nephritis (Glomerulitis)
- (2) Severe Lupus Nephritis (Glomerulonephritis)
- (3) Nephrotic and Pseudo nephrotic Syndrome in SLE

(1) Mild lupus nephritis (glomerulitis)—

Ten of the patients had mild involvement of the kidney when first studied. Eight patients were studied on subsequent occasions and a total of 21 studies was made. Initially local membranous glomerulitis was found in the kidneys of seven patients (§15-21) and proliferative glomerulitis in the kidneys of three (§12-14). In some of these ten patients mixed membranous and proliferative changes were found but the cases have been classified according to the predominant pathologic lesion. Clinically none of these patients had severe renal damage when first seen (Tables II and III), and at the time of their last study only one patient (§19) was ill with chronic renal failure. Her renal histology is described below.

The remaining nine patients had relatively good renal function after a period of study varying from 2 to 23 months but histologically a severe degree of damage was present in at least two (§18, 21). Since they have been under observation all these patients have had symptoms and signs of SLE with a varying clinical course. The disease has been characterized by severe acute exacerbations in three patients (§14, 18, 19) and has been more chronic in character in six (§13, 15, 16, 17, 20, 21). One patient (§13) had a number of acute exacerbations when first seen but the disease has now settled down. To predict renal involvement from the overall clinical course of the patient has proved impossible.

Below are recorded the histories of two of these patients, one (§13) whose renal disease has changed but slowly, the other (§19) whose course has been more rapidly downhill.

Case 13

In December 1951 M B: (R C F 303019) a 23 year old negro factory worker developed an erythematous skin rash on the face, chest and extensive surface of the fore arms. She had intermittent migratory joint pains. A diagnosis of SLE was made. In August 1952 she developed marked papilloedema and diplopia—a cerebral tumor was suspected and a craniot-

omy was done. No tumor was found. It was thought that her symptoms had been due to involvement of the lungs. SLE. Later a pleural effusion was reported. She was slightly anemic and had a leukocyte count of 10,000. Urinalysis and blood NPN were normal. In November there was electrocardiogram evidence of myocarditis and pericarditis. The liver and spleen were enlarged. Three months later she developed swelling of the feet, fever, anorexia, stiffness of her fingers and abdominal pain. She became very short of breath and was readmitted to hospital in February, 1953. There were bilateral pleural effusions and infiltration in the right lower lobe. There was a miliary calcareous and enlargement of the liver and lymph node. Diffuse alopecia of the scalp as noted. Proteinuria and casts appeared transiently in the urine. The thymol turbidity was elevated and many Hargreaves cells were found on examination of the bone marrow. There was a positive skin cell phenomenon. Treatment with ACTH resulted in clinical improvement and she was discharged from hospital on daily injections of ACTH. Later she was given cortisone.

In September she was readmitted to the hospital with pneumonia for pneumococcal pneumonia. A renal biopsy was done on September 30, 1953, at a time when renal blood NPN and tests of renal function were normal. Four months later she had an exacerbation of symptoms. She was febrile, had marked dyspnea at rest and vomiting. The pleural cavities were aspirated on several occasions. ACTH was given and her condition again improved. A second renal biopsy was done on February 1, 1954. Urinalysis, blood NPN and tests of renal function were normal.

Pericardial effusion was noted in July, 1954. She was admitted to the hospital for study. She had a moon face and a butterfly face rash. The fundi were normal and the blood pressure was 128/104 mm Hg. The serum calcium was normal. Protein was not found in the urine but many leukocytes were seen in the urinary sediment. The blood NPN and tests of renal function were normal. A renal biopsy was done on August 10, 1954. Cortisone and intermittent ACTH therapy were given when she was discharged from hospital.

In May, 1950, the physical examination was normal save for a mild conjunctivitis and the pigmented butterfly face rash. Urinalysis, blood NPN and tests of renal function were normal. A fourth renal biopsy was done on May 23, 1955.

First Biopsy (September 1953) A small fragment of renal cortex (5 glomeruli) but no medulla was included in the sections. The glomeruli were slightly shrunken and minimal to slight irregular thickening of the basement membrane was seen. There was slight focal hypercellularity but no adhesions were detected between the glomerular tufts and Bowman's capsule. Bowman's spaces contained a small amount of proteinaceous material. The collecting tubules were irregular in size; they contained a moderate amount of proteinaceous material and were lined by a slightly degenerated epithelium. There was a mild increase of interstitial fibrous connective tissue which contained a few small foci of inflammatory cells. In a few tubules hyaline casts were present. The small arteries were not remarkable.

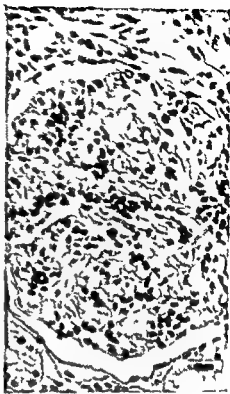
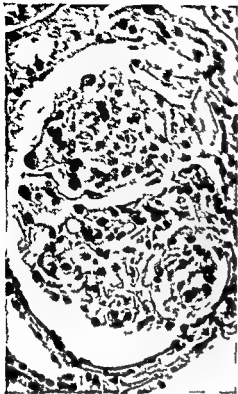
Diagnosis: Mild focal and generalized proliferative and membranous glomerulitis.

Second Biopsy (February 1954) (Fig. 6) Adequate renal cortex (18 glomeruli) and medulla were included in the sections. In general the glomeruli appeared shrunken and the lobular contour there was a distinct local hypercellularity due to endothelial proliferation. There was minimal focal thickening of the basement membrane in places.

Adhesions were noted between the glomerular tufts and Bowman's capsule but no epithelial crescents were present. The collecting tubules contained a small amount of proteinaceous material and the lining epithelium was mildly degenerated. The interstitial fibrous connective tissue was slightly increased and contained occasional inflammatory cells. The small blood vessels were congested and a few red blood cells had a definite sickle shape. No definite changes were detected in the walls of the small arteries.

Diagnosis: Local and generalized proliferative and membranous glomerulitis. A diagnosis of sickle cell trait was made. The diagnosis was confirmed by laboratory studies.

Third Biopsy (August 1954) Adequate renal cortex (16 glomeruli) and medulla were included in the sections. There was minimal sclerosis and slight focal thickening of the glomeruli.



COLOR PLATE—FIG 1 *Patient #12, First Biopsy, February 1954* Note the small areas of local hypercellularity at the periphery of the glomerular tuft. In these areas there is also mild smudgy thickening of the basement membrane (H&E \times 400)

COLOR PLATE—FIG 2 *Patient #19, First Biopsy, June 1955* Note there is an irregular rather severe fibrinoid thickening of the glomerular basement membrane. This is particularly prominent in the area of local necrosis seen on the right. Within this area the capillaries are obliterated, and hypercellularity and karyorrhexis are present (H&E \times 430). Compare Color Plate—Fig 3

COLOR PLATE—FIG 3 *Patient #19, Second Biopsy, February 1955* Note the fairly severe irregular smudgy thickening of the basement membrane. Above the glomerulus is adherent to Bowman's capsule, near the base of the adhesions poorly defined 'hematoxylin' bodies can be seen (H&E \times 430). Compare Color Plate—Fig 2

COLOR PLATE—FIG 4 *Patient #18 Fourth Biopsy, May 1955* Numerous areas of local hypercellularity can be seen throughout the glomerulus. There is a slight to moderate irregular thickening of the basement membrane (H&E \times 470). See also Fig 6



FIG 6 Patient #13 Second Biopsy, February 1954. There is slight lobulation of the glomerular tuft. Note the "muddy" basement membrane thickening and hypercellularity in local areas at the periphery of the glomerulus (H&E \times 450). See also Color Plate—Fig 4.

Many glomeruli were large and a distinct local hypercellularity was seen. Their basement membrane was only slightly thickened in some areas. No distinct "wire loop" lesions were noted. In a few areas within the glomeruli the hypercellularity was very marked and had caused complete obliteration of the capillary lumina. Karyorrhexis was noted in these areas. No adhesions were seen between the glomerular tufts and Bowman's capsules and no epithelial crescents were noted. No "hematoxylin" bodies were seen. The convoluted tubules contained a moderate amount of proteinaceous material. Their lining epithelium was mildly degenerated. A few hyaline cysts were noted within the collecting tubules. There was a mild sclerosis of the walls of all the arteries and arterioles. When compared with the previous biopsies there was a distinct increase in the severity of the glomerular damage.

Diagnosis: Local and generalized proliferative and membranous glomerulonephritis.

Fourth Biopsy (May 1955) (Color Plate—Fig 4): Adequate renal cortex (13 glomeruli)

in places but only minimal karyorrhexis and no "hematoxylin" bodies were seen. There were no adhesions between the glomerular tufts and Bowman's capsule, nor were epithelial crescents detected. There were mild degenerative changes of the epithelium of the convoluted tubules whose lumina contained a moderate amount of proteinaceous material. A few hyaline cysts were noted within the collecting tubules. The interstitial fibrous connective tissue was slightly increased and contained a few scattered inflammatory cells. There was a minimal degree of thickening of the wall of the small arteries and mild degenerative changes were seen therein but no fibrinoid was noted. Comparison with the previous biopsy showed no differences in the severity of the lesions.

Diagnosis Local and generalized proliferative and membranous glomerulonephritis

Case 19

In July 1953 BJ (R & E 400187) a cheerful 12 year old negro school girl developed pneumonia and a pericardial effusion. The pneumonia improved on treatment with penicillin but the pericardial effusion persisted. There was a history of intermittent episodes of fever and stiffness of the fingers and toes. In August she was referred to the University of Illinois Hospital. She was anemic, autely ill and had a high fever. A dark scaly eruption covered the whole thorax. The blood pressure was normal. The heart rate was rapid and there was electrocardiographic evidence of myocarditis. There were effusions into pericardial, pleural and peritoneal cavities. The liver, spleen and lymph nodes were all enlarged. Urinalysis was normal. The leucocyte count was normal. The thymol turbidity was 25 units, the cephalin flocculation was 4+ in 48 hours and many Hargraves cells were found on examination of the bone marrow. SLE was diagnosed and treatment with ACTH was started. She had a prompt clinical response, became afebrile and the pleural and pericardial effusions decreased. Cortisone was given after her discharge from hospital.

In December 1953 her symptoms returned, she was dehydrated, had lost weight and

was 33.6 units and the cephalin flocculation was 4+ in 48 hours. The blood NPN was normal. The GFR (C_{INULIN}) was 94 ml per minute, the RPF (C_{PAH}) was 514 ml per minute and the $T_{M_{PAR}}$ was 73 mg per minute. A renal biopsy was done on June 14, 1954.

Over the next seven months increasing amounts of protein were found in the urine. In January 1955 she was anorectic and lost 11 pounds in weight. The arterioles in the fundi were narrowed. The liver was enlarged, there was ascites and some peripheral edema. Many lymph nodes were enlarged. The serum albumin was 2.2 gm and the serum globulin 5.7 gm/100 ml. The blood cholesterol was 420 mg/100 ml. Gross proteinuria was noted and many leucocytes and granular and hyaline casts were found in the urine. Tests of renal function

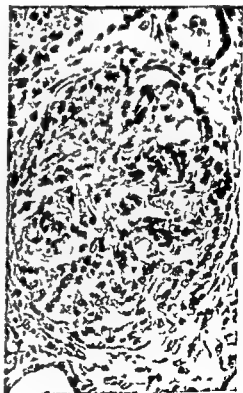
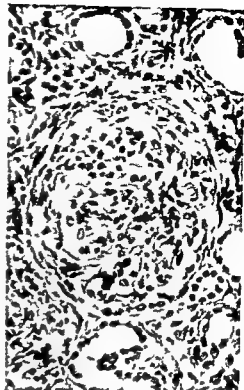
and medulla were included in the sections. Most glomeruli were definitely altered, they were somewhat lobulated, there was local and smudgy irregular thickening of their basement membrane suggesting fibrinoid changes. Wire loop lesions were noted in many

glomerulonephritis of Lohlein. In these areas karyorrhexis was noted but no hematoxylin bodies were seen. There were a few adhesions between the glomerular tufts and Bowman's capsules but no epithelial crescents were seen. The convoluted tubules varied somewhat in size, their lining epithelium was slightly degenerated and their lumina contained a small amount of proteinaceous material. There was a slight increase in interstitial connective tissue with minimal edema and infiltration of chronic inflammatory cells. Mild sclerosis and focal fibrinoid changes were seen in the small arteries. Mallory and PAS preparations confirmed these findings.

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COLOR PLATE—FIG 5 *Patient #2 Bony Ob 1953* Fibroid thickening of the glomerular basement membrane prominent throughout the glomerulus. There are nodular deposits (H&E × 500). See also Color Plate—Fig 6

COLOR PLATE—FIG 6 *Patient #1 Apy D mb 1953* Glomerulus from the autopsy specimen of the same patient. Color Plate—Fig 5 Note the large fibroepithelial cell content occupying much of Bowman's space. The glomerulus compressed. Hyaline and regular thickening of the glomerular basement membrane is present. Note the bulging of the edematous vessel lumen (H&E × 430)

COLOR PLATE—FIG 7 *Patient #51 F Bony Sp mbe 1953* The glomerulus obscured with case many areas of endothelial cell proliferation. The basement membrane markedly thickened and muddy. Note the epithelial cell proliferation at the periphery suggesting early restiformity. The interstitial tissue edematous. H&E × 430. Compare Color Plate—Fig 8 and Fig 8 and 9

COLOR PLATE—FIG 8 *Patient #91 S and Bony Ap 1 195* Note the severe glomerular thickening of the glomerular basement membrane obstruction of pass and excretion of the glomerular nodules. Widespread nodular glomerular. Note the fibroepithelial thickening and fibrosis of the interstitial tissue (H&E × 430). Compare Color Plate—Fig 7 and Fig 8 and 9

Diagnosis: Local and generalized membranous and proliferative glomerulitis

Section Biopsy (February 1955) (Color Plate—Fig 3) Six into renal cortex (five glomeruli) but no medulla were included in the sections. The glomeruli were ischemic and slightly lobulated. There were local areas of hypercellularity and of thickening of the basement membrane with the formation of wire loop lesions and in places obliteration of the capillary lumen. In some glomeruli the basement membrane was not only thickened but appeared smudgy and granular—suggestive of fibrinoid changes. In other glomeruli there was karyorrhexis and a few rather poorly defined hematoxylin bodies were seen. A few adhesions were noted between the glomerular tufts and Bowman's capsules in which a mild degree of fibroblastic proliferation was seen in places. There were moderate degenerative changes in the lining epithelium of the convoluted tubules whose lumina contained some proteinaceous material. A few hyaline casts were noted in the somewhat dilated collecting tubules and in the descending portion of Henle's loops. The interstitial tissue was normal. Minimal sclerosis of the walls of the small arteries was seen. These findings were confirmed in Mallory and PAS preparations.

*Diagnosis: Local and generalized membranous and proliferative glomerulonephritis**(2) Severe lupus nephritis (glomerulonephritis)—*

Twelve of the patients had severe involvement of the kidney when first studied. Eight patients were studied on subsequent occasions and a total of 26 studies was made. Initially local membranous glomerulonephritis was found in the kidneys of seven patients (#22-28), some of these had proliferative changes in addition. Subacute glomerulonephritis was found in the kidneys of four (#29-32) and chronic glomerulonephritis in one (#33). Clinically eight (#23, 24, 27, 29, 30, 31, 32, 33) had evidence of severe renal disease when first seen, and five have died, the other three are ill with chronic renal failure. Three of the remaining patients (#22, 25, 26, 28) had some evidence of impairment of renal function. Two died (#25, 26) of rapidly progressing renal failure two and twelve months after they were first seen. A third (#28) died of SLE within ten days. The fourth patient (#22) is chronically ill. Nine of these patients had generalized edema, and their illnesses are discussed in detail in section (3) Nephrotic and Pseudo nephrotic syndrome in SLE.

Below is recorded the history of one patient who died of chronic glomerulonephritis.

Case 31

A
tory
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1951
greatly but subsequently he had bouts of fever and arthritis five or more times a
month. In April 1951 three months later while still taking cortisone he developed chest pain
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was increased

Between September 1951 and his admission to the University of Illinois Hospitals in May 1953 he had received approximately 75 gm cortisone and 25 gm ACTH. Large purple

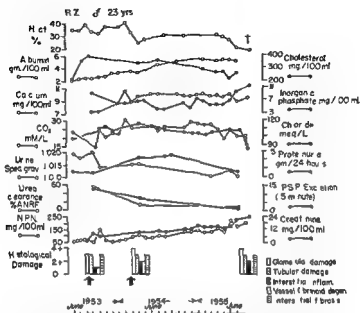
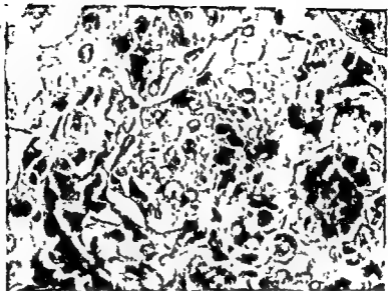


FIG 7 Patient #31 Chart illustrating the histologic changes in two biopsy specimens and one autopsy specimen and the changes in renal function and biochemical findings over a period of 26 months (see text)

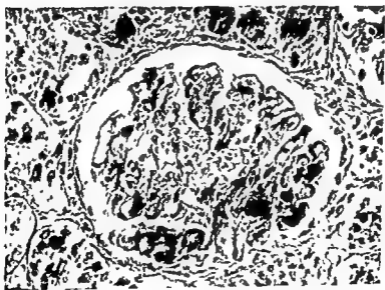
... 4 ggl from biopsy he was checked ... consisting of a high protein low salt diet calcium gluconate and sodium bicarb ... vomiting abdominal pain and breathing grand mal seizures hypertension seizures and positive Chvostek's sign The liver and lymph nodes were enlarged He was dehydrated and severely acidotic He was treated with blood and intravenous fluids and gradually improved

In April 1954 he was admitted to hospital for study Neither effusions into the serous ...

His diet was altered to provide 2000 calories and was low in potassium and protein He was also given sodium bicarbonate aluminum hydroxide gel calcium gluconate oral penicillin and multivitamins He was encouraged to drink large quantities of water especially



9



10

48

COLOR PLATE—FIG 9 *Patient #33 Postmortem Biopsy* Photomicrograph of a portion of a glomerulus. Note that the glomerular basement membrane is thickened and smudgy. The capillary lumina are almost obliterated in the central area. Note the hematoxylin bodies and slight karyorrhexis in this area. Below and to the right a small hyaline thrombus can be seen (H&E $\times 1100$).

COLOR PLATE—FIG 10 *Patient #20 Autopsy December 1953* This section was stained with Mallory-azun which colors the normal or hyalinized glomerular basement membrane blue. In this glomerulus note that the basement membrane is smudgy and stained a reddish color. This is typical of fibrosis. In the right lower quadrant small hyaline thrombi are present within the lumina of the capillaries (Mallory azun $\times 430$).

before bed time. On this regimen a daily urine output of between 1500 and 2500 ml was maintained.

From April 1954 to July 1955, his renal function steadily worsened and severe azotemia developed. During this period there were no clinical manifestations of SLE. Hargraves's cells were not found in the bone marrow or peripheral blood, the serum globulin and sedimentation rate fell to normal, and the thymol turbidity decreased. After sun bathing on July 4 1955, he developed a butterfly face rash, fever and swelling of his eyelids, and was admitted to hospital. Purpura uremic frost, hypertension and enlargement of the spleen were noted. He had severe anemia and leucopenia. On x ray of the abdomen the kidneys were small and appeared contracted. He was again given transfusions of whole blood, and his clinical state improved. When readmitted to hospital on August 8 he was short of breath and had been vomiting for three days. The blood pressure was 185/115 mm Hg. The heart was enlarged and there was a systolic murmur over the precordium. The liver was considerably enlarged, the spleen was palpable and there was a generalized lymphadenopathy. He was lethargic and restless. The hematocrit was 19%. There was oliguria and the urinary findings were unchanged. He died following two epileptiform convulsions. The NPN before death was 212 mg/100 ml.

Post-mortem examination revealed the following lesions: fibrous pericarditis and picuritis, perihepatitis and peripneumonitis, an old mitral valvulitis and fibrinoid degeneration of small arteries in the omentum and wall of the esophagus. There was no perivascular fibrosis in the spleen.

First Biopsy (September, 1953) (Color Plate—Fig 7) Adequate renal cortex (12 glomeruli) and medulla were included in the sections. The glomeruli were ischemic and lobulated. Marked diffuse and generalized hypercellularity was seen in the glomerular tufts. Their basement membranes were thickened and in some areas were smudgy and granular in appearance and the capillary lumina were obliterated. Epithelial crescents were present in many of the glomeruli; in others extensive adhesions were seen between the glomerular tufts and Bowman's capsule. A few small areas of karyorrhexis were noted but hematoxylin bodies were not found. The convoluted tubules were moderately atrophic. They contained a small amount of proteinaceous material. A few large pale blue-staining hyaline casts were seen in some of the collecting tubules. The interstitial tissue was edematous and many chronic inflammatory cells were scattered throughout it. There was a marked increase of fibrous connective tissue. Fibrinoid material was seen in the small arteries and arterioles whose walls were somewhat thickened. These findings were confirmed in Mallory and PAS preparations.

Diagnosis: Late subacute proliferative and membranous diffuse and generalized glomerulonephritis.

Second Biopsy (April 1955) (Fig 8 and Color Plate—Fig 8) Adequate renal cortex (20 glomeruli) and medulla were included in the sections. There was profound ischemia and marked lobulation of the glomeruli. Most of the glomeruli were either partially or completely fibrosed. In some instances this was due to marked thickening of the basement membrane. Local hypercellularity was seen in most of the glomeruli. Epithelial crescents were seen in many. In places fibrosis of Bowman's capsule was marked. The basement membranes were thickened, smudgy and granular, and in places its appearance was suggestive of fibrinoid. The convoluted tubules were atrophic. They were small, lined by a low cuboidal epithelium, and contained little or no proteinaceous material. A few rather large hyaline

preparations confirmed these findings.

Diagnosis Chronic proliferative and membranous, diffuse and generalized glomerulonephritis

Autopsy (August, 1955) (Fig 1) Many glomeruli were partially or completely hyalinized. In others there was marked thickening of the basement membrane which obliterated the capillary lumina in many places. 'Wire loop' lesions were seen in a few glomeruli. In many there was considerable proliferation of epithelial cells in both visceral and parietal layers of Bowman's capsule. A few fibroepithelial crescents were seen and adhesions between Bowman's capsules and glomerular tufts were common. The basement membrane in many glomeruli appeared smudgy and granular, but Mallory preparations did not confirm the presence of fibrinoid. There was slight leukorrhexis. No 'heart-shaped' bodies were seen. Most convoluted tubules were markedly atrophic, some were moderately dilated and filled with proteinaceous material or hyaline casts. There were advanced degenerative changes in the lining epithelium of these tubules and in Oil-Red O preparations abundant granular lipid was seen in the cells. There were similar changes in the loops of Henle and in the collecting tubules. There was marked fibrosis of the interstitial tissue which was infiltrated with chronic inflammatory cells. The walls of the small arteries and arterioles were severely sclerotic and hyalinized and their lumina were narrowed. No definite fibrinoid changes were seen in the vessel walls.

Diagnosis Chronic membranous and proliferative, diffuse and generalized glomerulonephritis

(3) *Nephrotic and pseudo-nephrotic syndrome in SLE—*

The criteria we have used for the diagnosis of the nephrotic syndrome in patients with SLE were the positive criteria of Leiter (166), namely, edema, massive proteinuria, low serum albumin, raised serum cholesterol, and an abnormal urinary sediment. By virtue of these criteria and clinical course, seven patients were diagnosed as having the nephrotic syndrome (#19, 23, 24, 25, 27, 29, 31—and Table V). Among the cases from the Pathology files, studied retrospectively, there was one (G II) in whom the clinical data fulfilled all criteria for the diagnosis of the nephrotic syndrome.

In contrast to this group of patients there were three edematous patients (#28, 30, 32—and Table VI) whose clinical course progressed rapidly to termination. They also fulfilled Leiter's criteria, save for the fact that their serum cholesterol levels were low. To characterize this group of patients whose illness was so acute and whose prognosis was so grave, we have coined the term "pseudo-nephrotic syndrome" (202). One other case (MO), who died with the pseudo-nephrotic syndrome, was found among the cases studied retrospectively from the Pathology files.

A NEPHROTIC SYNDROME. Among the patients with the nephrotic syndrome, five were women and three were men. Their ages ranged from 13 to 46 years. In two the blood pressure was significantly elevated. Three had persistent gross hematuria, and all the others had microscopic hematuria. Hyaline and granular casts were found in all, and fatty casts, doubly refractile bodies, or oval fat bodies in five.

In general, proteinuria persisted, but the quantity passed varied day by day. The nitrogenous constituents of the plasma slowly increased, the concentrating power of the kidney decreased, and there was a parallel deterioration of the urea clearance and PSP excretion. The serum cholesterol ranged between 369 and

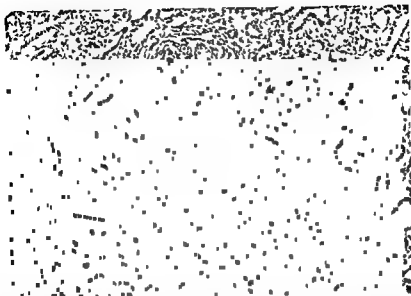


FIG 8 Patient #31 *Second Biopsy April 1950*, Low power view. Note edema, fibrosis and infiltration of chronic inflammatory cells in the interstitial tissue. The tubules are atrophic. There is increased cellularity of the glomeruli. Epithelial crescents are also seen (H&E \times 180). Compare Fig 9 and Color Plate—Fig 7 and 8.

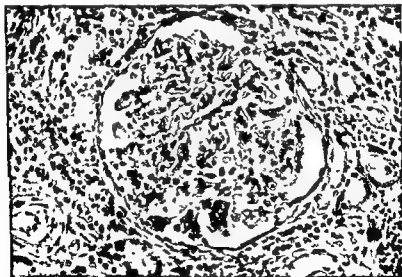


FIG 9 Patient #31 *Autopsy August 1955*. Note the severe thickening of the glomerular basement membrane and the irregular distribution of endothelial and epithelial cell proliferation. The adjacent convoluted tubules are atrophic and the interstitial tissue is infiltrated by chronic inflammatory cells. In other areas fibrosis and hyalinization of the glomeruli were prominent (H&E \times 370). Compare Fig 8 and Color Plate—Fig 7 and 8.

TABLE V

Clinical and laboratory data from eight patients with SLE and the nephrotic syndrome

Patient	Age Sex	Edema	B P	Urine			Serum			Onset of Edema	Present Status	
				Protein*	Red cells	Casts	Fat†	Albumin	Cholesterol			Cholinesterase
								gm/100 ml	mg/100 ml	S.P.H. units/h		
#19 B I	13 F	+++	110/80	++++	Micro	Hyaline Granular	N I	2.2	425	—	January 1955	Alive Azotemic and hypopertensive
#23 I N	33 F	++++	160/90	7-23/0	Cross	Hyaline Granular RBC	Casts DRB	2.7	425	0.90	March 1954	Died January 1955 Renal failure
#24 W II	46 M	+++	150/90	9.2	Micro	Hyaline Granular Cellular	N I	2.4	460	0.92	June 1955	Alive Chronic renal failure
#28 R N	70 F	+++	180/120	3.0	Cross	Hyaline Granular	Casts DRB	2.4	440	—	April 1955	Died May 1955 Renal failure
#27 M P	27 F	++++	132/8	++++	Cross	Hyaline Granular Cellular	N I	2.0	369	—	January 1955 During pregnancy	Died May 1955 Renal failure and acute pancreatitis
#29 R C	34 F	++++	141/90*	++++	Micro	Hyaline Granular	Casts DRB	2.9	420	1.17	September 1955	Alive Chronic renal failure
#31 H Z	61 M	+++	140/100	2.4-10.7	Micro	Hyaline Granular RBC	Casts DRB	2.4	480	—	May 1952	Died August, 1955 Renal failure
G B ‡	23 M	+++	110/5	++++	Micro	Hyaline Granular RBC WBC	Casts DRB	2.1	471	—	April 1954	Died June 1954 Renal failure

* Counts per 24 hours or per 12 hours

† DRB = doubly refractile bodies

‡ Case studied postmortem only

471 mg/100 ml and in none did it exceed 500 mg/100 ml. As we shall show below, the development of the renal lesions in this group of patients—as in other patients with lupus nephritis—was associated with a suppression of many of the manifestations of SLE. In particular, we have confirmed Brenner's observation (35) that skin lesions may be absent in the presence of the nephrotic syndrome. Three of these patients are alive (three months to three years after the onset) and two are slowly becoming increasingly azotemic. The other four died from two months to three years after the onset of edema. All died as a result of their kidney disease, except patient #27 who suddenly developed acute pancreatitis when she was already severely ill from renal failure.

At the time of the initial histologic study, membranous glomerulonephritis was seen in four, subacute glomerulonephritis in three. Case #19 developed the nephrotic syndrome at the time of her second biopsy which showed membranous and proliferative glomerulonephritis. When serial histologic studies were done (#23, 25, 27, 29, 31) the lesions were found to have progressed in all

TABLE VI
Clinical and laboratory data for patients with SLE and the
post-nephrotic syndrome

Pa. no.	Age	Sex	Edema	BP	Urine				Serum			Onset of Edema	Date and Cause of Death
					Protein	Red Cells	Ca ⁺⁺	U ₁₀	Albumin (mg/100 ml)	Cholesterol (mg/100 ml)	Cholesterol (mg/100 ml)		
#28 AW	26 F	+++	2.80	++++	5.0	Co. ua Hya. no Gran. ls	DRB OFI	2.6	65		No em be 1951	Novem be 1954	
#30 BB	2 F	+++	170	0	+++	Gross	Hya. no Co. ua Ca. s	Waxy Ca. s (DRB)	1.7	6.9	30	October 1954	Febru ary 1955
#31 BD	18 F	+++	10.80	4.2		Gross	Hya. no G. anula RBC	DRB OFB	2.2	172		July 1954	Novem ber 1954
101	3	++++	0.5	+++		Mico	Gross Hya. no	Ca. s Hya. no	2.4	0.5		July 1954	June 1954

Cams per 24 h
DRB = double red cells
Ca. s = calcium
Hya. no = hyaline
G. anula = granular
RBC = red blood cells
OFB = oil field bodies

In cases #23 and #27 membranous glomerulonephritis progressed to subacute glomerulonephritis
The points listed above are illustrated in the following cases

Case 3

Since 1949 F. D. I. (E. J. 1951) (Fig 10) a 33 year old female had had Raynaud's phenomenon in mild December 1953 she developed an erythema to stretch of the neck and extensor surface of the forearms This disappeared within two weeks Later she noted a slow enlargement of the forearms This was accompanied by mild nodules was noted These signs and symptoms subsided spontaneously within two weeks In February 1954 swelling of the left ankle occurred and there were pains in the shoulders elbows and knees Edema appeared and progressed to involve feet face and hand
On March 23 she returned to the hospital and was admitted to another hospital after a general relapse and an enlarged spleen The blood pressure was 120/80 mm Hg The hemoglobin was 3.7 and the white count 4000/mm³ There was gross proteinuria and a proteinuria of 1.7 gm/day The sedimentation rate was 102 mm/hr The total serum protein was 4.0 gm/100 ml The Wassermann test was negative No Targatess cells were found on examination of the bone marrow She had positive pleuritic pain The fevered and splenomegaly were spontaneous She was sent home to rest in bed Gross hematuria developed in June she noted that her liver was falling out
One month later she was hospitalized to the University of Illinois Hospital She was a female there was stiffness in the eyes the lymph nodes were slightly enlarged but the liver and spleen were not palpable The blood pressure and optic fund were normal A systolic murmur was heard at the apex Crossed hematuria was noted and 7 gm protein was

TABLE V

Clinical and laboratory data from eight patients with SLE and the nephrotic syndrome

Patient	Age Sex	Edema	B P	Urine				Serum			Onset of edema	Present Status
				Protein*	Red cells	Casts	Fat†	Albumin	Cholesterol	Cholin esterase		
								gm/100 ml	mg/100 ml	Δ pH units/hr		
#19 B J	48 F	+++	110/80	++++	Micro	Hyaline Granular	Nil	2.2	425	—	January 1955	Alive Azotemic and by pertension
#23 I C	31 F	++++	160/90	7-23 0	Gross	Hyaline Granular RBC	Casts DRB	2.7	325	0.90	March 1954	Died January 1955 Renal failure
#24 W H	46 M	+++	150/90	9 3	Micro	Hyaline Granular Cellular	Nil	2.6	460	0.85	June 1953	Alive Chronic renal failure
#25 R N	29 F	+++	180/170	3 9	Gross	Hyaline Granular	Casts DRB	3.4	410	—	April 1955	Died May 1955 Renal failure
#27 M P	27 F	++++	132/78	++++	Gross	Hyaline Granular Cellular	Nil	3.0	360	—	January 1955	Died May 1955 Renal failure and acute pancreatitis
#20 R C	34 F	++++	144/92	++++	Micro	Hyaline Granular	Casts DRB	2.9	470	1.17	September 1952	Alive Chronic renal failure
#31 R Z	21 M	++++	160/105	2 4 10 7	Micro	Hyaline Granular RBC	Casts DRB	2.4	460	—	May 1952	Died August 1955 Renal failure
G B ‡	38 M	++++	110/75	++++	Micro	Hyaline Granular RBC WBC	Casts DRB	3.1	471	—	April 1954	Died June 1954 Renal failure

* Grams per 24 hours or plus casts

† DRB = doubly refractile bodies

‡ Case studied postmortem only

manifestations of SLE. In particular we have confirmed Brenner's observation (35) that skin lesions may be absent in the presence of the nephrotic syndrome. Three of these patients are alive (three months to three years after the onset) and two are slowly becoming increasingly azotemic. The other four died from two months to three years after the onset of edema. All died as a result of their kidney disease, except patient #27 who suddenly developed acute pancreatitis when she was already severely ill from renal failure.

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systolic murmur over the precordium. The liver, spleen and lymph nodes were not enlarged. Urinary studies were unchanged. The urine specific gravity was fixed at 1010. The blood NPN and blood creatinine had increased to 41 and 47 mg/100 ml respectively. She had hypercholesterolemia (CO 18 mM/L, cholesterol 127 mg/L). The serum albumin was 3.6 and the globulin 1.8 gm/100 ml. The serum cholesterol was 376 mg/100 ml. Many *E. coli* and *Haemolytic streptococci* were cultured from the urine. A renal biopsy was done on February 7, 1955.

Follow-up on the hospital. In July, 1955 her clinical condition was unchanged. She had azotemia and hypercholesterolemia. The liver and spleen were again enlarged. Cross-hematuria persisted. She became short of breath and complained of tiredness and was admitted to hospital with a hematocrit of 19%. These symptoms improved after transfusion of one liter of blood. The urinary findings were unchanged but the blood creatinine increased to 79 mg/100 ml and the non-protein nitrogen to 81 mg/100 ml. A fourth renal biopsy was made on September 10.

Final follow-up on the hospital. From September to November, 1955 she had severe menorrhagia and also polycythemia. She had dyspnea on exertion, paroxysmal nocturnal dyspnea and complaints of severe headaches. On examination the blood pressure was 210/110 mm Hg, the liver was enlarged, purpuras and hemorrhages and slight peripheral edema were noted in the extremities. The hematocrit was 20%—the bleeding time was prolonged to 10 1/2 minutes and the prothrombin time was increased, indicating the presence of a possible hepatic or circulating anticoagulant. The blood creatinine was 97 mg/100 ml and the CO₂ combining power was 17 mEq/liter. She was treated with a low sodium, low protein diet, pentolium reserpine and chlorpromazine.

Final follow-up on the hospital. In December, 1955 she had been vomiting for one week. The liver and spleen were no longer palpable. The urine contained protein 4+, many erythrocytes, 5-8 leucocytes and many granular and cellular casts. *Potomysis*, *abula* and *enococci* were cultured from it. The blood creatinine was 11.8 mg/100 ml and the blood NPN was 103 mg/100 ml. She had an episode of acute lupus peritonitis with adynamic ileus (2/9). Treatment consisted of intravenous hydrocortisone 600 mg daily. Thereafter her condition gradually deteriorated and she died on January 11, 1956.

At the post-mortem examination there was serofibrinous pericarditis and pleurisy, generalized meningitis and aneurysms. The left atricle was enlarged and the liver and spleen were both enlarged. The kidneys were moderately contracted and there was a bilateral polycystic disease.

First Biopsy (July 1955). Adequate renal cortex (5 glomeruli) and medulla were included in the sections. A moderate thickening of the basement membrane of the glomeruli was seen. There appeared some hyaline casts in places. Wire loop lesions were noted but there was no evidence of fibrous change in the basement membrane. Neither hypercellularity of the glomeruli nor adhesions were noted. A small amount of proteinaceous material was present in Bowman's spaces. The lining epithelium of the convoluted tubules was moderately degenerated and a small amount of proteinaceous material was seen in the lumen. Interstitial fibrosis and edema were slight. Minimal glomerular changes were seen in the walls of the small blood vessels.

Discussion: Local and generalized membranous glomerulonephritis

Second Biopsy (October 1955) (Fig. 11). Adequate renal cortex (glomeruli) and medulla were included in the sections. The glomeruli were profoundly altered with rather severe sclerotic changes and hypercellularity. The basement membrane was moderately thickened and some large, great loop lesions were noted. There were a few adhesions between the glomeruli and Bowman's capsules but no epithelial crescents were noted. In an occasional glomerulus hypercellularity was seen but no hematoxylin bodies were present. A very small amount of proteinaceous material was present in some of Bowman's spaces. There was a rather marked atrophy of the convoluted tubules whose lining epithelium was confined to scattered segments. The tubular interstitium contained a moderate amount

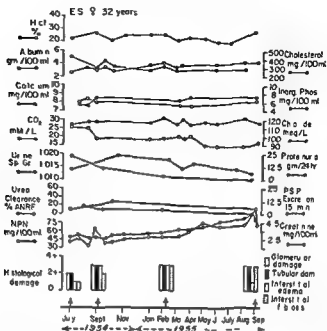


FIG 10 Patient #23 Chart illustrating the histologic changes in four biopsy specimens and the changes in renal function and biochemical findings over a period of 13 months. The patient died in January 1956 (see text)

found in a 24 hour urine specimen. Many leucocytes and numerous hyaline granular and fatty casts were seen in the sediment. The hematocrit was 21%, the leucocyte count was normal and the ESR was raised. The blood NPN and BUN were 41 and 21 mg/100 ml respectively.

167 ml/min, and the T_{MPAN} was 7 mg/min. She was kept in bed, the sodium in her diet was restricted but she received no steroids. A renal biopsy was made on July 11. Gross hematuria persisted.

Second admission to the hospital. In September she became febrile and had abdominal pain and a recurrence of ankle edema. On readmission to the hospital anasarca and pallor were noted. The blood pressure was 160/90 mm Hg. There was a right pleural effusion and ascites. The liver was tender and both liver and spleen were enlarged. The left ankle was painful, red and swollen. The hematocrit was 20%. There was gross hematuria and proteinuria. Many leucocytes, doubly refractile bodies, hyaline granular fatty and erythrocyte casts were found in the urine. Renal function was severely impaired. The NPN and BUN were slightly raised. The total serum protein was 5.4 gm/100 ml (albumin 3.5 globulin 1.9 gm/100 ml). The serum cholesterol was 375 mg/100 ml. The Coombs and Wassermann tests were negative. The thyroxine turbidity was 47 units. *F. coli* and an *hemolytic enterococcus* were grown from the urine. She was kept in bed, the sodium in her diet was restricted and tetracycline was given. Marked improvement followed. Her temperature became normal. The spleen and liver were not palpable. The edema subsided and the urine became sterile. A renal biopsy was done on October 5.

Third admission to the hospital. At the time of the third admission to hospital in February 1955 she had malaise and persistent gross hematuria. There was periorbital edema but no ankle edema. She was pale. The blood pressure and optic fundi were normal. There was a

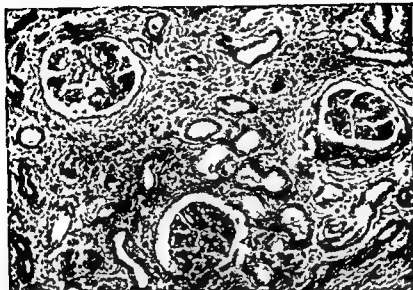


FIG 12 Patient #23 Third Biopsy February 1955 The glomerular basement membrane is diffusely thickened and "wire loops" are seen in places There is no glomerular hypercellularity Note the fibroepithelial crescent in the glomerulus on the right The interstitial connective tissue is edematous fibrosed and infiltrated by numerous chronic inflammatory cells The tubules are atrophic (H&E \times 225)

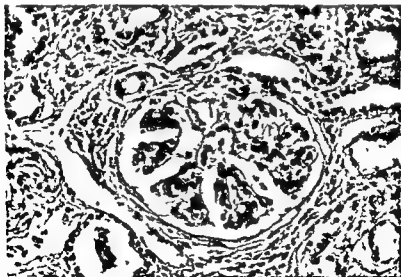


FIG 13 Patient #23 Fourth Biopsy September 1955 The glomerulus is isolated Note the smudgy thickening of the glomerular basement membrane and the clumping of endothelial cells The interstitial tissue is fibrotic and edematous The tubules are atrophic (H&E \times 430)

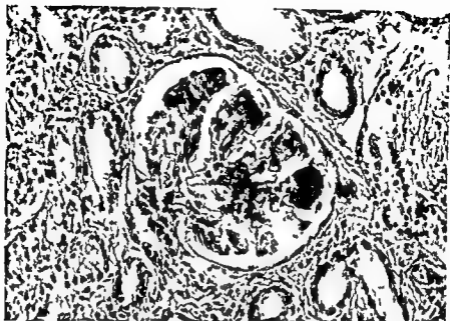


FIG 11 Patient #23 Second Biopsy, October 1954 The glomerulus is lobulated. Note the endothelial cell proliferation and smudgy basement membrane thickening in areas throughout the glomerulus. The interstitial tissue is edematous and the tubules are somewhat atrophic (H&E \times 430)

of proteinaceous material. Hyaline casts were noted within some of the collecting tubules. The interstitial fibrous connective tissue was rather markedly increased and edematous and was infiltrated by a considerable number of chronic inflammatory cells. In places changes suggestive of fibrinoid were seen in the small arteries.

Diagnosis Subacute local and generalized, membranous and proliferative glomerulonephritis and superimposed interstitial nephritis

Third Biopsy (February 1955) (Fig 12) A small fragment of renal cortex (3 glomeruli) but no medulla was included in the sections. The glomeruli were somewhat lobulated and markedly ischemic. A diffuse somewhat smudgy thickening of the basement membrane

degenerative changes of the lining epithelium were seen. They contained a relatively small amount of proteinaceous material and in places a few hyaline casts. The interstitial fibrous connective tissue was markedly increased and edematous. It was infiltrated by a large number of chronic inflammatory cells. There was moderate thickening and sclerosis of the walls of the small blood vessels.

Diagnosis Early chronic diffuse and generalized membranous glomerulonephritis with superimposed interstitial nephritis

Fourth Biopsy (September, 1955) (Fig 13) Adequate renal cortex (7 glomeruli) and medulla were included in the sections. The glomeruli were ischemic and lobulated and a rather severe and diffuse thickening of their basement membrane was seen. There was local hypercellularity, 'wire loop' lesions and questionable fibrinoid changes were seen. No proteinaceous material was seen in Bowman's spaces. Many Bowman's capsules were

Diagnosis Chronic diffuse and generalized membranous glomerulonephritis, superimposed acute suppurative and chronic pyelonephritis

Case 29

RC (R&E 415'65), a 34 year old housewife had migratory arthritis intermittent fever, and anorexia since 1919. For the next two years she suffered from pleuritic pain. In August 1952 while vacationing in Florida she developed an erythematous rash of the face neck and elbows. Lesions of lupus erythematosus were found in a section of a biopsy of skin and Hargraves cells were seen on examination of the blood. The following month swelling of the ankles appeared. In May, 1954 she was admitted to hospital and found to have the nephrotic syndrome due to SLE. The eyelids were puffy and there was much pretibial edema bilateral pleural effusions and ascites. The liver was enlarged the blood pressure was 150/98 mm Hg but the optic fundi were normal. The urine contained considerable protein and many hyaline granular fatty and erythrocyte casts. Renal function was impaired. The blood NPN was 69 mg/100 ml. The serum albumin was 2.9 gm/100 ml and the serum cholesterol was 380 mg/100 ml. Treatment with hydrocortisone resulted in clinical improvement and the edema subsided. The dosage was reduced when she developed a toxic psychosis.

In July she had recurrence of arthritis and pleuritic pain. She complained of a diffuse alopecia of the scalp. On admission to the University of Illinois Hospitals for study in September the blood pressure was 141/72 mm Hg and there was no edema. There was much protein in the urine and leucocytes and many hyaline granular and fatty casts were seen in the sediment. There was impairment of renal function. A renal biopsy was done on September 28. Sealy erythematous lesions developed on the skin and regressed following treatment with chloroquin.

In February 1955 she had a streptococcal pharyngitis and fever arthritis and pleurisy. Penicillin was given and resulted in an improvement of her symptoms. Two weeks later she was admitted for study. The blood pressure was 130/84 mm Hg. Urinalysis was unchanged. The blood NPN was 45 mg/100 ml. Later the liver and spleen became enlarged. She was readmitted to hospital in June. There was no peripheral edema. The blood pressure was 160/90 mm Hg and grade II hypertensive retinopathy was found on funduscopic examination. A third renal biopsy was done on June 21. Urinalysis was unchanged at this time.

First Biopsy (June 1955) Adequate renal cortex (5 glomeruli) and very little medulla were included in the sections. The glomeruli were markedly ischemic and somewhat lobulated. There was distinct local hypercellularity due to endothelial cell proliferation and a local irregular thickening of the basement membrane in a few glomeruli. In these same areas there was slight karyorrhexis but no hematoxylin bodies were seen. There were numerous adhesions between the glomerular tufts and Bowman's capsules. No epithelial crescents were noted. Bowman's spaces contained a small amount of proteinaceous material and Bowman's capsules were slightly fibrotic. The convoluted tubules were atrophic in places and their lining epithelium was moderately degenerated. Their lumina contained small amounts of proteinaceous material. The interstitial fibrous connective tissue was moderately increased and slightly edematous with moderate infiltration of chronic inflammatory cells. There was mild thickening of the walls of the small arteries and changes suggestive but not diagnostic of fibroid degeneration were seen therein. Mallory and PAS preparations confirmed these findings. In Oil Red-O preparations of frozen sections a considerable amount of finely granular lipid material was noted within the cells of the convoluted tubules. Gomori's preparations for alkaline phosphatase in frozen dried material disclosed the presence of very small amounts of the enzyme within the cells of the convoluted tubules.

Diagnosis Late subacute local and generalized membranous and proliferative glomerulonephritis

Second Biopsy (September 1955) Adequate renal cortex (8 glomeruli) and medulla were included in the sections. The glomeruli were ischemic and somewhat lobulated. Partial hyaline sclerosis was seen in many due to fusion of thickened basement membranes.



FIG 14 Patient #23 Autopsy January 1950 Note the severe diffuse thickening of the glomerular basement membranes Fibrinoid changes and hyalinization are present in the glomerulus on the right Slight local hypercellularity is seen The tubules are atrophic and the interstitial connective tissue is fibrosed Elsewhere there was evidence of acute suppurative and chronic pyelonephritis (H&E \times 340)

thick and fibrotic neither epithelial crescents nor glomerular adhesions were seen The interstitial fibrous connective tissue was markedly increased and slightly edematous and there was a diffuse infiltration of chronic inflammatory cells The tubules were markedly atrophic and contained occasional hyaline casts but little or no proteinaceous material The tubular epithelium was slightly degenerated The small arteries were slightly to moderately sclerotic In O1 Red O preparations only minimal fatty degeneration of the tubular epithelium was noted

Diagnosis Early chronic diffuse membranous and local proliferative glomerulonephritis with superimposed interstitial nephritis

Autopsy (January 1950) (Fig 14) Many glomeruli were partially or completely hyalinized others were ischemic and lobulated There was a severe diffuse thickening of their basement membranes which in places appeared smudgy and granular suggestive of mild

aceous material hyaline casts and many polymorphonuclear leucocytes were found within the dilated tubules There were considerable degenerative changes of and abundant granular lipid was seen within the lining epithelium of the convoluted tubules There was fibrosis and

but no fibrinoid changes

and lymph nodes were enlarged. The left wrist, left elbow, and left ankle were painful red and swollen. There was 3+ protein in the urine and erythrocytes = few leukocytes and many hyaline and granular casts in the sediment. The blood NPN was 34 mg/100 ml, the serum cholesterol was 109 mg/100 ml, the albumin was 3.0 gm/100 ml, and the globulin was 3.0 gm/100 ml. The serum sodium was 129 meq/L, and the chloride was 96 meq/L. The Wassermann test was positive. Many Hargreaves cells were found on examination of the peripheral blood. There was x-ray evidence of right pleural effusion. SLE was diagnosed. Symptomatic improvement followed on treatment with 100 mg cortisone daily.

On December 15 she became febrile and acutely ill and was readmitted to hospital. There was edema of the eyelids and legs, a macular face rash, and enlargement of all the lymph nodes. The blood pressure was 150/90 mm Hg. Bilateral pleural effusions were found. There was a tachycardia and evidence of myocarditis on the electrocardiogram. Protein, many leukocytes, a few erythrocytes, and many granular and hyaline casts were found in the urine. The serum albumin was 2.6 gm/100 ml. The hemoglobin was 8.4 gm/100 ml, and the NPN was 49 mg/100 ml. When treated with tetracycline and increased doses of cortisone she improved remarkably and became asymptomatic. The dosage of cortisone was reduced to 75 mg daily on discharge from the hospital. One week later she was readmitted with acute abdominal pain and ankylosing spondylitis. The rash was still present and the renal arterioles in spasm. The blood pressure was 190/100 mm Hg. The abdomen was rigid. There were rebound tenderness and hyperactive bowel sounds. The liver and lymph nodes were enlarged.

There was gross proteinuria and gross hematuria. The urinary specific gravity was fixed at 1.010. Many leukocytes and hyaline granular and leukocytic casts and doubly refractile bodies were seen in the urine. The blood NPN was 110 mg/100 ml. Renal function was severely impaired. The serum albumin was 1.7 gm/100 ml, the serum cholesterol was 130 mg/100 ml, and the serum cholinesterase was 0.38 Δ pH units per hour. The Wassermann test was negative. Many Hargreaves cells were found on examination of the bone marrow. The dosage of cortisone was increased to 100 mg/day. She became afebrile and the hematuria ceased. The blood NPN fell to 47 mg/100 ml.

On January 19, 1955, a renal biopsy was done and subacute glomerulonephritis was diagnosed. E coli was grown repeatedly from the urine, but culture of the renal tissue was sterile. She was discharged from the hospital and continued to take cortisone at home. However, two weeks later on February 7 she was readmitted with pulmonary edema. The blood pressure was 105/110 mm Hg, the pulse was rapid, and a gallop rhythm was found. She was anemic and was passing frank blood in the urine. The blood NPN was 81 mg/100 ml. She was acutely ill. The serum potassium was 7.5 meq/l. She expired a coma three days later.

Renal Biopsy (January 19, 1955) (Fig. 15). Sections included a small fragment of renal cortex (6 glomeruli) but no medulla. The glomeruli were ischemic, some had lobulated and hypercellular tufts. There was a local irregular thickening of the basement membrane. In some glomeruli partial hyaline cast on the tuft was noted. In places the thickened basement membrane was smudgy and granular, strongly suggesting fibrinoid. In other glomerular tufts were loop lesions were seen. Bowman's capsules were thickened and fibroid. Epithelial cell proliferation formed crescents in Bowman's spaces which contained moderate amount of juxtaglomerular material. There was considerable atrophy and degeneration of the lining epithelium of the collecting tubules. The renal cortex contained much proteinaceous material. Hyaline casts were noted in a few of the collecting tubules. There was rather marked interstitial fibrosis with some edema and considerable infiltration of chronic inflammatory cells. Slight to moderate thickening and sclerosis of the wall of the small arteries was seen with clings of fibroid Mallory and PAS preparations confirmed the presence of fibroid material in the glomeruli.

Diagnosis: Late subacute lobular glomerulonephritis.

Autopsy (February 19, 1955) (Fig. 16 and 17). The glomeruli were moderately hypercellular, lobulated, and ischemic. In many the tufts were compressed by large fibroid material.

and obliteration of capillary lumina. A few areas of hypercellularity were present. There were many adhesions between the glomerular tufts and Bowman's capsules which were thickened and fibrosed. A few "wire loop" lesions were seen, but no definite fibrinoid changes were detected within the glomeruli. Neither epithelial crescents nor "hematoxylin" bodies were seen. Marked atrophy and rather severe degenerative changes were seen in the lining epithelium of the convoluted tubules. Their lumina contained a moderate amount of proteinaceous material. There was a marked increase of the interstitial fibrous connective tissue which was slightly edematous and contained numerous areas of chronic inflammatory cells. A few tubules contained hyaline casts. Slight sclerosis and some fibrinoid changes were noted in the walls of the small arteries. Mallory and PAS preparations confirmed these findings. Comparison with the previous biopsy revealed a marked increase in the severity of the lesions. Interstitial fibrosis and atrophy of the tubules was more marked and the fibrosis of the glomeruli had progressed.

Diagnosis: Chronic local and generalized membranous and proliferative glomerulonephritis superimposed interstitial nephritis.

Third Biopsy (June, 1955) Adequate renal cortex (11 glomeruli) and medulla were included in the sections. Some of the glomeruli were completely hyalinized. In others there was a rather diffuse and severe thickening of the basement membrane and "wire loop" lesions were seen. There was little or no evidence of glomerular hypercellularity. Bowman's spaces were free of proteinaceous material and contained no epithelial crescents. There was either moderate atrophy or some dilation of the convoluted tubules. They contained a small amount of proteinaceous material and were lined by a slightly degenerated epithelium. A few hyaline casts were noted in the collecting tubules. The interstitial fibrous connective tissue was moderately increased in areas and was infiltrated by chronic inflammatory cells. Slight to moderate sclerosis was noted in the walls of the small arteries but no definite fibrinoid changes were seen.

Diagnosis: Chronic local and generalized membranous glomerulonephritis.

B PSEUDO-NEPHROTIC SYNDROME The four patients who died of SLE with lupus nephritis and the pseudonephrotic syndrome were all young women who were critically ill throughout their disease (Table VI). None of them lived longer than five months, and two (case #28 and M O) died within a few weeks of their first symptoms. Two cases (#28 and 30) were treated with ACTH and cortisone, but to no avail. One patient (case #28) died of myocarditis and renal disease. The other three patients died in renal failure and uremia. Oliguria was present, but none was anuric. When first admitted to the hospital, all these patients were edematous and looked "nephrotic." They were pale, their faces were swollen, and their eyes were puffy. It was, therefore, with some confidence that a clinical diagnosis of the nephrotic syndrome was made, and the finding of abnormally low serum cholesterol levels occasioned some surprise. However, the other laboratory data—save for the low serum cholinesterase level in case #30—were consistent with what is usually found in the nephrotic state.

Case 30

BS (R & E 42717), a 27 year old negro factory worker enjoyed good health until July 1954 when she had supraorbital headaches and was found to be anemic. One month later

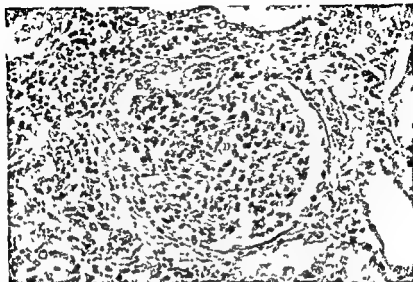


FIG. 17. *Latent #30 Autopsy February 1965.* The glomerulus is adherent to Bowman's capsule in a few places. Note the smudgy thickening of the glomerular basement membrane and a small area of karyorrhexis. The vascular spaces around the glomerulus are congested (H&E $\times 340$).

crecenta. In others there was irregular local thickening of the basement membrane although no typical wire loop lesions were noted. In a few smudgy granular fibrinoid changes were noted in the basement membrane. In a few glomeruli considerable karyorrhexis was seen but no 'hematoxylin' bodies were detected. There was a moderate to severe interstitial fibrosis with considerable edema and infiltration of chronic inflammatory cells. The convoluted tubules were either atrophic or dilated. Their epithelium was low cuboidal and degenerate. Their lumina contained proteinaceous material and occasional hyaline casts. The small blood vessels were congested. Occasional focal fibrinoid changes were noted in the slightly thickened walls of the small arteries. Mallory and PAS preparations confirmed the presence of fibrinoid material in the glomeruli and in the walls of the arterioles. Oil Red-O preparations disclosed the presence of fairly abundant granular lipid material in the epithelium of the convoluted tubules. Comparison with the biopsy revealed some increase in the severity of the lesions particularly in the degeneration of the tubules.

Diagnosis: Late subacute diffuse and generalized proliferative and membranous glomerulonephritis.

This case presents rather strikingly the severe involvement of the kidneys noted in the patients ill with the pseudo nephrotic syndrome and lupus nephritis. The clinical state and course of the patients parallels in severity the degree of renal damage. The type of lesions seen in these patients is also shown in Color Plate—Fig. 9 (Case #32).

Assessment of the histologic analysis given in Table IV indicated that proliferative and basement membrane changes were not strikingly different in the nephrotic and pseudo nephrotic groups. However with respect to 'hyaline' thrombi, 'wire loop' lesions, karyorrhexis and the presence of 'hematoxylin'



FIG 15 Patient #30 Biopsy January 1955 Note the epithelial and fibroepithelial crescents There is partial hyalinization of some glomeruli Some hypercellularity and irregular thickening of the glomerular basement membrane is also present Note the interstitial fibrosis and edema and the atrophy of the tubules in many areas (H&E $\times 200$)

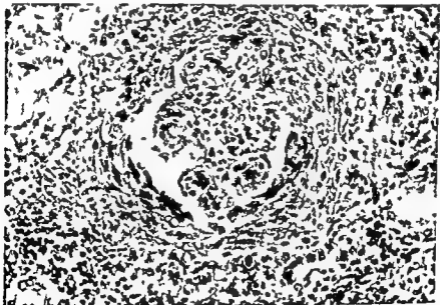


FIG 16 Patient #30 Autopsy February 1955 Bowman's space is almost filled by a fibroepithelial crescent which completely surrounds the glomerulus The glomerular basement membrane is smudgy and irregularly thickened The per glomerular tissue is infiltrated by a large number of chronic inflammatory cells (H&E $\times 340$)

TABLE VII

An analysis of the nature and severity of the renal lesions in 40 abnormal biopsy and 9 autopsy specimens from 33 patients with SLE*

Histologic Features Analyzed	(A) Biopsies (40 specimens)					(B) Autopsies (9 specimens)				
	Grades of damage				Total number abnormal	Grades of damage				Total number abnormal
	4+	3+	2+	1+		4+	3+	2+	1+	
Glomeruli										
Basement membrane thickening	0	10	17	13	40	2	7	0	0	9
Wire loop [†] lesions	0	3	10	16	29	0	5	4	2	9
Fibrinoid	0	1	8	21	30	1	2	3	2	8
Hypercellularity	1	4	9	15	29	0	3	3	3	9
Local necrosis	0	1	2	10	13	0	0	0	5	5
Karyorrhexis	0	0	5	6	11	0	1	3	3	7
Hematoxylin [†] bodies	0	0	2	2	4	0	2	1	0	3
Hyaline [†] thrombi	0	0	0	0	0	0	2	0	1	3
Capillary adhesion	1	3	4	8	16	0	2	5	0	7
Crescents	0	0	3	0	3	0	1	2	0	3
Ischemia	0	13	7	18	38	0	4	4	1	9
Protein in Bowman's space	0	0	4	26	30	0	3	1	6	7
Total glomerular damage	1	12	10	11	40	6	2	1	0	9
Tubules										
Degeneration	0	8	15	16	39	0	8	1	0	9
Atrophy	2	1	7	12	22	1	1	0	5	7
Dilatation	1	0	19	8	28	0	0	3	1	4
Protein in tubular lumina	0	1	15	23	39	0	3	4	2	9
Casts in tubular lumina	0	3	6	14	23	0	2	3	3	8
Total tubular damage	1	10	9	16	36	2	5	2	0	9
Interstitial tissue										
Edema	0	3	7	9	19	0	3	2	4	9
Fibrosis	0	4	6	18	28	0	2	2	4	8
Inflammation	0	2	5	16	23	1	2	3	2	8
Arteries										
Sclerosis	0	0	5	20	25	0	0	3	3	6
Fibrinoid	0	0	4	13	17	0	1	2	3	6

* Cases studied clinically and pathologically.

of the lesions enumerated above was graded from 0 (normal) to 4 plus (extremely severe and affecting all or almost all of the appropriate structures). The details of these analyses are set forth in Tables IV and VII.

(2) Terminology—

The pleomorphism and patchy character of the lesions of lupus nephritis made

bodies and fibrinoid degeneration the affection of the glomeruli was more common and more severe in the pseudo nephrotic group (Color Plate—Fig 9)

2 PATHOLOGIC MATERIAL

A Criteria for histologic analysis and definition of terms

In diffuse disorders of the kidneys such as diabetic glomerulosclerosis or proliferative glomerulonephritis it is unusual to find that all nephrons are affected by the disease process. Many are spared and even in those nephrons that are involved the glomeruli are not damaged in a uniform manner. The histologic picture is uneven and the lesions can be seen to be in different stages of development. This was also found to be true for lupus nephritis. In the early stage of the disease at least three glomeruli out of every five were seen to be damaged but they were not affected to the same degree. As the disease progressed more and more glomeruli were involved and the lesion became more diffuse but still uneven in its development. The irregularity of the process made careful evaluation of the sections most important lest the degree of damage be assessed incorrectly or erroneous interpretations arise. For these reasons among others a fine systematic analysis was made of each biopsy or autopsy studied. Details of the analysis and grading are given below. In essence this was a semi-quantitative histologic study which allowed us to reduce inherent errors to a minimum. It permitted us to make a nice assessment of the type and degree of structural damage in each section; it allowed us to compare—in detail—the findings in serial studies of the same patient and was to prove useful in comparing the degree of structural change with data from tests of renal function. In this study of patients with lupus nephritis it was apparent that an adequate renal biopsy reflected accurately the type and degree of pathology in the kidneys. In the nine cases which were studied both by biopsy and at postmortem excellent correlations were noted between the detailed analyses of the histology in the biopsy and in the autopsy specimens.

(1) Methods of analysis—

On each specimen observations and assessments were made with respect to the following structures and pathologic entities. Glomerular damage was assessed as a whole and the following glomerular structural changes were assessed individually: thickening of the basement membrane; increase in cellularity of the tuft (endothelial or epithelial); hyaline thrombi; wire loop lesions; karyorrhexis; hematocytin bodies; fibrinoid changes in the glomerular basement membrane; local necrotic lesions; adhesions of the glomerulus to Bowman's capsule and fibroepithelial crescents. The congestion or ischemia of the tuft were also evaluated. Tubular damage was also assessed as a whole and the tubular changes observed and evaluated were: degeneration, atrophy, and dilatation. The number of casts in the tubular lumen was also noted. The presence of proteinaceous material was sought both in Bowman's spaces and in the tubular lumen. In the interstitial tissue the changes evaluated were: the presence of edema, of fibrosis, and of infiltration with inflammatory cells. In the vessel walls sclerotic changes and fibrinoid degeneration were noted. In each case the severity

TABLE VII

In analysis of the nature and severity of the renal lesions in 40 abnormal biopsy and 9 autopsy specimens from 53 patients with SLE*

Histologic Features Analyzed	(A) Biopsies (40 specimens)					(B) Autopsies (9 specimens)				
	Grades of damage				Total number abnormal	Grades of damage				Total number abnormal
	4+	3+	2+	1+		4+	3+	2+	1+	
Glomeruli										
Basement membrane thickening	0	10	17	13	40	2	7	0	0	9
Wire loop lesions	0	3	10	16	29	0	3	4	2	9
Fibroid	0	1	8	21	30	1	2	3	2	8
Hypocellularity	1	4	0	15	20	0	3	3	3	9
Local necrosis	0	1	2	10	13	0	0	0	5	5
Karyorrhexis	0	0	5	6	11	0	1	3	3	7
Hematoxylin bodies	0	0	2	2	4	0	2	1	0	3
Hyaline thrombi	0	0	0	0	0	0	2	0	1	3
Capsular adhesions	1	3	4	8	16	0	2	5	0	7
Crescents	0	0	3	0	3	0	1	2	0	3
Ischemia	0	13	7	15	35	0	4	4	1	9
Protein in Bowman's space	0	0	4	26	30	0	0	1	0	1
Total glomerular damage	1	12	16	11	40	6	2	1	0	9
Tubules										
Degeneration	0	6	15	16	37	0	6	1	0	7
Atrophy	2	1	7	12	22	1	1	0	5	7
Dilatation	1	0	15	8	24	0	0	3	1	4
Protein in tubular lumina	0	1	15	23	39	0	3	4	2	9
Casts in tubular lumina	0	3	6	14	23	0	2	3	3	8
Total tubular damage	1	10	9	16	36	2	5	2	0	9
Interstitial tissue										
Edema	0	3	7	9	19	0	3	2	4	9
Fibrosis	0	4	6	15	25	0	2	2	4	8
Inflammation	0	2	5	0	23	1	2	3	2	6
Arteries										
Sclerosis	0	0	5	20	25	0	0	3	3	6
Fibrosi	0	0	4	13	17	0	1	2	3	6

* Cases studied clinically and pathologically.

of the lesions enumerated above was graded from 0 (normal) to 4+ (extremely severe and affecting all or almost all of the appropriate structures). Details of these analyses are set forth in Tables IV and VII.

(2) Terminology—

The pleomorphism and patchy character of the lesions of lupus nephritis

the selection of precise and descriptive diagnostic terms quite difficult. Nonetheless in this study it was imperative to use accurate albeit cumbersome terminology.

The following terms were chosen because they seemed to us to represent more accurately the character and degree of the histologic changes.

Glomerulitis was used to indicate a proliferative and/or a membranous lesion of the glomerular tufts in the absence of any significant tubular damage or changes in the interstitial tissue.

Glomerulonephritis was used to indicate a proliferative and/or a membranous lesion of the glomeruli associated with tubular and/or interstitial tissue changes.

In both glomerulitis and glomerulonephritis the distribution and degree of lesions was specified by adding one or two of the following descriptive terms.

1) *Local* referring to a glomerulitis or glomerulonephritis characterized by lesions affecting one or more areas within each glomerulus.

2) *Diffuse* referring to lesions affecting diffusely each involved glomerulus.

3) *Focal* referring to lesions either local or diffuse affecting only some glomeruli.

4) *Generalized* referring to lesions either local or diffuse affecting all or almost all glomeruli.

(5) *Material*—

In the present study are included 57 biopsy and nine autopsy specimens from 33 patients. The detailed histologic analysis for each specimen from each patient is set out in Table IV. A summary of the histologic findings is set forth in Table VII A and B.

The slides from 21 cases of SLE in the files of the Pathology Departments have also been reviewed and the same methods of analysis described above were used to study them (Table IX). In addition 15 autopsy cases of glomerulonephritis were studied by the same methods (Table X). These analyses were compared with those from patients with lupus nephritis (Table XI).

B. *The renal lesions in cases studied by biopsy*

(1) *The glomerular lesions*—

Thickening of the glomerular basement membrane. The glomerular basement membrane is normally a thin delicate eosinophilic structure which is colored purplish red with the PAS technique and blue with the aniline blue of the Mallory

known that the thickness of the basement membrane may vary within a wide range in perfectly normal glomeruli. This is probably the result of distention or retraction of the basement membrane resulting from congestion or ischemia of the glomerular tuft and was taken into account before establishing the degree of basement membrane thickening especially in the early stage of lupus nephritis.

Thickening of the glomerular basement membrane was present in all 40 of



FIG. 18 Patient #1? Second Biopsy May 1955 Note the local thickening of the glomerular basement membrane especially at the periphery of the glomerular tuft. The smudgy appearance of the thickening suggests the presence of fibrin clots. In the areas of thickening note the slight but definite hypercellularity due to clumping and/or proliferation of endothelial cells (H&E \times 500)

normal biopsy and in all nine autopsy specimens. It was more severe in the autopsy specimens as might be expected. The thickening of the basement membrane was usually local rather than diffuse, the peripheral portions of the glomerular tuft being more commonly affected (Fig. 18). When present at least 50 per cent of the glomeruli were usually affected. A diffuse regular thickening of the glomerular basement membrane similar to that seen in membranous glomerulonephritis was observed only very late in the disease. The severity of the thickening varied considerably in different areas of the same glomerulus (Fig. 19) and from one glomerulus to another. As it increased around various capillary loops the capillary lumen proportionately decreased in size and contained fewer red blood cells. In some cases the capillary lumen became completely obliterated in patches (Fig. 20). No evaluation of basement membrane thickening was made when the glomeruli were partially or completely hyalinized. Complete hyalinization was most unusual and was seen only twice (Fig. 21).

Wire loop lesions were seen in 29 biopsy and all nine autopsy specimens. The incidence and severity of wire loop lesions was greater in the autopsy material. The lesions were usually not observed unless the thickening of the glomerular basement membrane was at least of moderate severity (2+ or greater). The involved capillary loops appeared stiff and rigid (Fig. 22). Early in the disease they were seen in the peripheral portion of the glomeruli, later,



FIG 10 *Patient #2? Second Biopsy June 1955* Note a fairly diffuse but irregular thickening of the glomerular basement membrane and narrowing of the capillary lumina. Note also on the left the well organized adhesion between the glomerular tuft and Bowman's capsule (H&E $\times 480$)

although they were more common at the periphery, they were seen in some cases throughout the glomerular tuft. Slight to moderate fibrinoid changes were found in all but four of the sections in which "wire loop" lesions were seen.

Fibrinoid changes The presence of fibrinoid changes in the glomerular basement membrane and in the walls of the small arteries was recognized or at least suspected by the smudgy granular strongly eosinophilic appearance of the involved structures in H&E stained sections (Color Plate—Fig 2 and 5). The affected areas appeared more irregular and less dense or "stiff" than comparable lesions resulting from hyaline or amyloid deposition. Confirmation of the fibrinoid change was obtained in Mallory preparations in which the involved basement membrane stained a reddish color contrasting with the blue of the uninvolved connective tissue (Color Plate—Fig 10). In the PAS preparations fibrinoid stained a particularly intense red purple color. With milder changes (+) the special staining reactions were not as specific. Fibrinoid changes were found more commonly in the glomeruli than in the small arteries and arterioles and were seen in 30 biopsy and in eight autopsy specimens.

Proliferative changes in the glomerular tuft Varying degrees of hypercellularity were noted in 29 biopsy and nine autopsy specimens. Evaluation of proliferative changes presented considerable difficulty especially in the early stages of the disease when the degree of hypercellularity was slight. Sections cut above or below 5 microns—the section thickness used consistently in this study—may

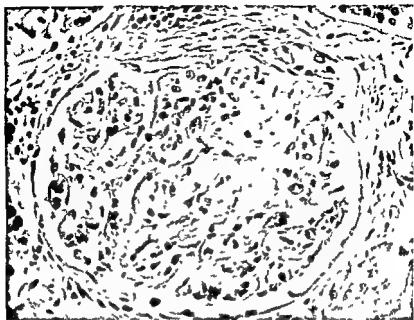


FIG 20 Patient #25 Autopsy May 1950 Note in one area that the thickening of the glomerular basement membrane is severe there is complete obliteration of the capillaries and early hyalinization Elsewhere in the glomerulus the basement membrane is only moderately thickened (H&E $\times 500$)



FIG 21 Patient #53 Biopsy, July 1955 Partial and complete hyalinization of glomeruli in advanced lupus nephritis In the glomerulus at the left severe diffuse basement membrane thickening can still be recognized This degree of hyalinization of glomeruli is unusual even in advanced lupus nephritis (H&E $\times 250$)



FIG 22 Patient #78 Biopsy June 1956 Note the diffuse but irregular thickening of the glomerular basement membrane. Distinct wire loops can be seen especially at the periphery of the glomerular tuft. Note that at the involved capillary loops appear at first slightly smudgy (H&E $\times 400$)

lead to over- or under-evaluation of the degree of glomerular cellularity. When hypercellularity was present in the milder lesions it was almost exclusively noted in the peripheral portion of the glomerular tuft (Color Plate—Fig 1) as it increased in severity it tended to become more diffuse (Fig 23) and was often associated with varying degrees of glomerular lobulation. Local thickening of the basement membrane or fibrinoid changes or both were observed frequently in the areas of hypercellularity. In almost all cases the increased number of cells in the glomerular tufts appeared to be due to endothelial rather than epithelial proliferation. It was only in the more advanced stages of lupus nephritis that epithelial cells appeared to have increased in number either in the visceral or in the parietal layer of the glomerulus. Reduction in the size of glomerular capillaries due to hyaline or fibrinoid changes led to a conglutination and apparent increase of endothelial cells in some areas. This was taken into account before determining the degree of hypercellularity.

Local necrosis of the glomerular tuft. A small local area of necrosis in the peripheral portion of the glomerulus was one of the lesions considered strongly suggestive and almost pathognomonic of lupus nephritis (Color Plate Fig 2 and Fig 38 and 40). This lesion was seen in one or more glomeruli in 13 biopsy and five autopsy specimens. It was characterized by local areas of basement membrane thickening with obliteration of capillaries, fibrinoid changes and early necrosis, a few lymphocytes and occasionally polymorphonuclear leuko-



FIG 11 ■ Pat 11475 Biopsy June 195, Note the marked hypercellularity of the glomerulus due to proliferation of the endothelial cells. The basement membrane thickening is mild and is obscured except in a few areas by the cellular proliferation. This type of diffuse glomerulitis is not common in lupus nephritis (H&E \times 370)

ocytes were seen. Karyorrhexis of endothelial, epithelial and inflammatory cells was an almost constant feature of the lesion and hematoxylin bodies were observed in about one third of them. These local necrotic lesions resembled closely those which occur in embolic glomerulonephritis of Lohlein. By contrast with embolic glomerulonephritis necrosis was not as prominent, inflammatory cells were less numerous and microorganisms were never observed, even in sections especially prepared to demonstrate bacteria. Karyorrhexis was common to both embolic glomerulonephritis and lupus nephritis but the presence of hematoxylin bodies was considered quite characteristic for lupus nephritis. The nature of the local and focal glomerular necrosis in lupus nephritis is not well understood.

Hematoxylin bodies were observed in only four biopsy and three autopsy specimens. They were found only within glomeruli in association invariably with karyorrhexis and usually with fibrinoid changes (Color Plate—Fig 9 and Fig 40). They were rounded or oval structures of approximately nuclear size or smaller; they stained dark lavender to purplish red with hematoxylin in contrast with the blue black color of the nuclei. Additional stains used for the identification of hematoxylin bodies included iron hematoxylin (black) and pyronine (purple red). These special staining reactions were not found to be essential for their identification.

Hyaline thrombi which occluded the lumina of the glomerular capillaries

were observed in three autopsy specimens and were not seen in the biopsy specimens. They were rounded or elongated cylindrical structures homogeneous and strongly eosinophilic (Color Plate—Fig 9 and 10). They filled more or less completely the lumen of the capillaries and frequently were attached to the capillary wall. These thrombi reacted in a strongly positive manner in PAS preparations and stained red in Mallory Azan preparations. No red blood cells were seen within them nor were they thought to participate in their constitution. The staining properties and general appearance of hyaline thrombi made differentiation from superficially similar capillary lesions such as those observed in diabetic glomerulosclerosis quite easy. The material constituting hyaline thrombi although not exactly identified histochemically, was certainly more closely related to fibrin or fibrinoid than to hyaline. It appears to us that in this context the term hyaline should be abandoned in favor of fibrin or fibrinoid.

Capsular adhesions. Adhesions between the glomerular tufts and Bowman's capsules were observed in 16 biopsy and in seven autopsy specimens. In the early stage of their development thin strands of smudgy or smooth hyaline material were seen. As these syncytiae became larger they involved progressively larger areas of the surface of the glomerular tuft and eventually formed well developed fibrous adhesions (Color Plate—Fig 3). Frequently the process was accompanied by a certain degree of retraction and distortion of the glomerulus. Adhesions developed particularly in relation to areas of local hypercellularity or necrosis of the glomerular tuft (Fig 39 and 40)—evidently as a result of inflammatory alterations at the periphery of the glomerulus.

Fibro epithelial crescents were noted in three biopsy and in three autopsy specimens (Color Plate—Fig 6 and Fig 15 and 16). They were always associated with capsular adhesions. They did not differ significantly from the fibro epithelial crescents seen in the common variety of subacute glomerulonephritis.

Glomerular ischemia. The number of red blood cells present in the capillaries of the glomerular tuft was evaluated. Our criteria in this evaluation were based on our experience of approximately fifty biopsy specimens of essentially normal kidneys. Grades from 0 to 4+ indicate progressively severe degrees of glomerular ischemia. It was seen in 38 abnormal biopsy specimens and in nine autopsy specimens. The presence of ischemia was thought to be significant only when associated with other lesions of the glomerulus.

Overall glomerular damage. After each element in the glomerulus had been analyzed independently an estimate of total glomerular damage was made. The degree of glomerular damage was graded in the usual manner taking into consideration not only the severity of the lesions but also the proportion of affected glomeruli. Various degrees of glomerular damage were found in 40 biopsy and in nine autopsy specimens. As expected the incidence and severity of the glomerular lesions was greater in the autopsy specimens.

(2) Tubular lesions—

The state of the renal tubules was also evaluated. As in many renal diseases the changes observed in the tubules in the various stages of lupus nephritis were

not specific. An accurate analysis was made only of the changes seen in the proximal and distal convoluted tubules since renal medulla was present in approximately fifty per cent of the biopsies. In biopsy material the appearance of the tubular epithelium, even in the normal kidney, was different from that usually seen postmortem. As a rule in biopsy specimens the free margin of the epithelial cells was more irregular and there was greater variation in the height of the cells. As a result the size of the tubular lumen also varied. The cause of the irregularity of the free margin is not known. It may be the result of the trauma of the biopsy needle. Another possible explanation is that it is due to the varying activity of the cell and represents absorption of protein and solutes. The varying height of the epithelium may represent varying states of diuresis (28, 135, 181). These features peculiar to biopsy material made the evaluation of tubular damage more difficult.

Degeneration of the tubular epithelium was found in 37 biopsy and nine autopsy specimens. Various features were taken into consideration. The following features were commonly found: swelling of the cells with or without vacuolization of their cytoplasm and an excessive irregularity and fraying of the free margin of the cells with loss of the brush border (Fig. 39 and 40). In a few cases in which Oil-Red O preparations for lipids were made vacuolization was seen to be due to fat droplets. Occasionally finely divided lipid material was observed in tubular cells in which vacuolization was not evident in H&E preparations. At times the cytoplasm of the tubular cells contained eosinophilic 'hyaline' granules. These rarely gave a strongly positive reaction in PAS preparations. These granules may represent the results of tubular protein reabsorption (210, 211). In a few cases the Gomori technique was used to stain alkaline phosphatase in the tubules. It appeared to us that the concentration of this enzyme was decreased proportionately to the degree of tubular degeneration. Evaluation of this feature was difficult because of the lack of a sufficient number of normal control biopsy specimens and because of the observation that even in normals there was a considerable variation in the concentration of alkaline phosphatase in the tubular cells.

Atrophy of the convoluted tubules was judged by the reduction in the size of the tubules and in the number and size of their cellular components. Pyknosis of nuclei was frequently associated with cellular atrophy. As a rule the tubular basement membrane was thickened in those cases in which atrophy was severe. Tubular atrophy was observed in 22 biopsy and seven autopsy specimens (Fig. 12, 14 and 15).

Dilatation of tubules was observed in 24 biopsies and in four autopsy specimens. As a rule dilatation was found only in some groups of nephrons while others were atrophied (Fig. 8 and 21). It never reached the proportions seen so commonly in chronic renal disease particularly pyelonephritis.

Proteinaceous material was present in Bowman's spaces (Fig. 40) and in the lumina of the convoluted tubules in varying amounts even in renal tissue from patients whose urine was free of significant amounts of protein. At times the eosinophilic amorphous or granular proteinaceous material appeared to be in

direct continuity with the irregular free border of the tubules and with the cytoplasm of the epithelial cells of Bowman's capsule and of the tubules. However in many cases the protein precipitate appeared to be free in the lumen and its amount was roughly proportional to the degree of proteinuria (see also Table XIII).

Casts The casts seen within the tubules were usually hyaline less commonly granular and infrequently cellular in type. Fatty thrombyotic casts were seen in only one case (#23). As a rule the casts stained a deep red purple color with PAS. Occasionally they were quite large and had a waxy appearance. They seemed to be more numerous in the collecting tubules. Occasionally casts were observed in biopsy specimens which were otherwise entirely normal.

Overall tubular damage The estimate of total tubular damage was made after the above features were analyzed. The tubules were damaged in varying degrees in 36 biopsy and nine autopsy specimens and were significantly more severe in the latter.

(3) Interstitial tissue—

The appearance of the interstitial tissue received considerable attention. It is in our opinion *the forgotten tissue component of the kidneys* and abnormalities therein may have greater functional significance than is generally thought (5, 89). The three basic abnormalities observed in the interstitial fibrous connective tissue were edema, fibrosis and inflammation. Edema was found in 19 biopsy and in all nine autopsy specimens. It was characterized by a swelling of the connective tissue with resulting separation of fibrillar and cellular elements and often a change in staining quality. The normal eosinophilia was usually decreased and in patchy areas of several biopsies a pale gray blue color was noted suggestive of alterations in the mucopolysaccharides of the ground substance (Color Plate—Fig. 6). In general edema was noted in the relatively early stages of lupus nephritis and reached its maximum in the subacute stage of the disease (Fig. 8). Varying degrees of fibrosis were noted in 28 biopsy and in eight autopsy specimens. The degree of fibrosis was related to the chronicity of the disease. As the disease process became more chronic a greater density and occasionally hyalinization of the fibrous connective tissue was observed (Fig. 12 and 14). PAS and Mallory preparations were useful in evaluating these changes more accurately. When present both interstitial edema and fibrosis were patchy in distribution especially in the cortex and as a rule were seen in areas where the glomeruli were more severely damaged.

Interstitial infiltration of inflammatory cells was noted usually in the moderately advanced or advanced stages of the disease and was found in 23 biopsy and eight autopsy specimens. It was characterized by relatively small numbers of lymphocytes, plasma cells and histiocytes located as a rule in the areas of fibrosis and edema (Fig. 8). Perivascular distribution of interstitial edema, fibrosis and inflammatory cells was not a striking feature. Occasionally large infiltrates were observed which were often periglomerular especially when acute lesions were present in the glomeruli (Fig. 16). In a few cases a superimposed infection was suggested by the large number and distribution of in-

flammatory cells and by the presence of neutrophils and eosinophils. This interpretation was reinforced on occasion by positive bacterial cultures obtained from renal tissue at the time of biopsy. Neither definite fibrinoid changes nor 'hematoxylin' bodies were observed in the interstitial fibrous connective tissue.

(4) Vessels—

As a rule a few small arteries and arterioles could be recognized in each biopsy specimen. In general the vascular changes were not impressive. The most common arterial lesion was fibrosis of the wall with or without hyalinization and mild narrowing of the lumen. Sclerosis of the vessel wall was present in 20 biopsy and six autopsy specimens. A significant degree of vascular sclerosis was seen only in the more advanced and chronic stages of lupus nephritis. Fibrinoid changes in the vessels were carefully searched for and were observed in 17 biopsy and six autopsy specimens. However they were of significant degree (2+ or 3+) in only four biopsy and three autopsy specimens (Fig 24). The presence of fibrinoid in these cases was confirmed by the staining properties of this material in PAS and Masson preparations. In general fibrinoid was less commonly observed in the walls of small arteries and arterioles than in the glomeruli.

C. The character and distribution of renal lesions

When the detailed analysis was completed a pathologic diagnosis was made for each biopsy and each autopsy specimen using the descriptive terminology

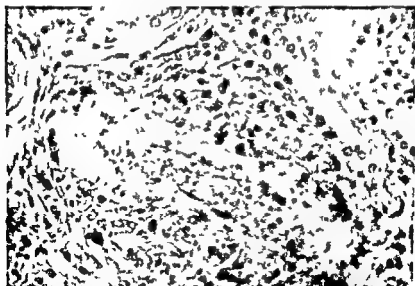


FIG 24 Case of SLE from postmortem series (R.E. Autopsy 130/1960) Small renal artery. Note severe fibrinoid changes involving most of the vessel wall. There are a few inflammatory cells in the perivascular tissues (H&E \times 330).

TABLE VIII

*The type and distribution of the renal lesions in lupus nephritis
in 40 abnormal biopsies and 9 autopsy specimens*

Histology of Lupus Nephritis	Glomerulitis	Glomerulonephritis	
	15 biopsies and no (0) autopsy specimens	25 biopsies specimens	9 autopsy specimens
1 Type of lesion			
(a) Membranous	6	■	■
(b) Proliferative and membranous	6	3	0
(c) Membranous and proliferative	3	12	7
(d) Subacute	0	4	3
(e) Chronic	0	■	2
2 Distribution of lesions in glomerulus			
(a) Local	15	20	5
(b) Diffuse	0	■	4
3 Distribution of lesions throughout section			
(a) Focal	5	3	0
(b) Generalized	10	22	9

defined above. In Table VIII are grouped the various diagnoses according to the character and distribution of the lesions. Glomerulitis was found in 15 biopsy specimens but was not seen in any autopsy specimen. The lesions within each glomerulus were local in all cases with glomerulitis, and in most of those with glomerulonephritis. Diffuse lesions were noted late in the course of the disease only in five biopsy and four autopsy specimens. Focal lesions affecting a few glomeruli were found only in five sections with glomerulitis and in three with glomerulonephritis. Thus in the majority of cases the lesions affected all or almost all the glomeruli—even when the renal lesions were in an early stage.

In all abnormal sections examined glomerular basement membrane thickening was seen. Associated proliferative changes were noted in 25 biopsy and seven autopsy specimens. Proliferative changes were slightly more predominant among the biopsies with glomerulitis, changes in the basement membrane predominated among the biopsy and autopsy specimens with glomerulonephritis.

In 15 of the 34 specimens diagnosed as lupus glomerulonephritis the histologic picture was either subacute (seven cases) or chronic lupus glomerulonephritis (eight cases). The histopathologic criteria used to diagnose the subacute and chronic glomerulonephritic stages of lupus nephritis were not significantly different from those used to diagnose the common types of subacute and chronic glomerulonephritis. In the subacute stage, however, the glomerular changes of lupus nephritis were still prominent in most cases. In the chronic stage the changes were less suggestive of lupus nephritis, and in some cases the changes of lupus nephritis could not be recognized.

When the histologic findings were analyzed for severity and type of lesions no differences were noted with age, sex, or race. No relationship was noted between the duration of symptoms and signs of SLE and the severity of the

renal lesions. However, once the renal lesion was established it was progressive in most instances.

D The renal lesions in cases of SLE studied postmortem

In order further to evaluate the findings in the renal biopsies the kidneys of 21 autopsy cases from the files of the Departments of Pathology were studied. These cases were selected because they had had the characteristic clinical features of SLE during life, and because there was pathologic evidence of SLE in organs other than the kidneys. The findings are set out in Table IX. Many

TABLE IX
*In analysis of the nature and severity of the renal lesions
in 20 autopsy specimens from patients with SLE**

Histologic Features Analyzed	Grades of Damage				Total Number Abnormal
	++	+	±	1+	
Glomeruli					
Basement membrane thickening	2	7	6	5	20
Wire loop lesions	1	7	3	5	12
Fibrinoid	1	2	4	2	9
Hypercellularity	2	1	8	9	19
Local necrosis	0	0	4	2	6
Karyorrhexis	0	0	3	4	7
Hematoxylin bodies	0	0	0	5	5
Hyaline thrombi	1	0	2	3	6
Capsular adhesions	1	2	2	6	11
Crescents	2	0	2	4	8
Ischemia	0	0	8	2	10
Protein in Bowman's space	0	0	2	5	7
Total glomerular damage	4	8	4	4	20
Tubules					
Degeneration	8	6	8	4	18
Atrophy	8	0	1	12	13
Dilatation	0	0	3	8	11
Protein in tubular lumina	1	1	11	7	20
Casts in tubular lumina	0	2	3	8	13
Total tubular damage	1	5	10	4	20
Interstitial tissue					
Edema	0	1	4	10	15
Fibrosis	0	0	2	11	13
Inflammation	8	3	3	10	16
Arteries					
Sclerosis	0	0	1	10	11
Fibrinoid	0	2	2	1	5

* Cases studied from the files of the Departments of Pathology, 1933-1956.

of the cases in this group had died with clinical evidence of severe renal involvement.

It is apparent (Tables VII, IX, and XI) that the incidence and severity of the renal lesions was considerably greater in the autopsy than in the biopsy specimens. This was true of almost all features analyzed. Lesions such as hematoxylin bodies and hyaline thrombi were definitely more common in the autopsy than in the biopsy specimens. This may perhaps be explained by the fact that a far larger number of glomeruli was available for study in autopsy slides. On the other hand, lesions such as local necrosis were only slightly more frequent in autopsy specimens.

In one instance the kidney was histologically normal. Seven had lupus glomerulitis and thirteen were diagnosed as lupus glomerulonephritis. Of the latter group seven had subacute lupus glomerulonephritis and in no case was chronic lupus glomerulonephritis found. Basement membrane changes and cellular proliferation were noted in 12 cases; changes in the basement membrane without proliferative changes were seen in eight. As was expected, the histo-



FIG. 25 (a) Patient #30. Autopsy February 1955. Portion of external surface of a kidney in severe subacute lupus glomerulonephritis. The capsule has been removed. Note the swollen appearance and the distinct mottling of the organ. A few punctate hemorrhages can be seen.



FIG. 25 (b) *Int. et 430 Autopsy February 1955* Section through the same kidney. Note the mottling of the swollen cortex. The corticomedullary junction is distinct.

logic abnormalities in the kidneys had progressed to an advanced stage in a large proportion of those who had died.

Grossly the kidneys were heavier than normal and appeared swollen, pale and mottled (Fig. 25). A mild contraction of the kidney was seen in very few specimens (Fig. 26). This is in agreement with the experience of other investigators who have remarked on the rarity of contraction of the kidneys in SLE. Ten of the 21 autopsies were done between 1943 and 1950, the remainder from 1951 to 1956. The lesions were distinctly more severe in the later group. This may be related to prolongation of life due to treatment of patients with ACTH and steroid hormones. A separate comparison was also made between the nine autopsy specimens from cases clinically studied and treated by us and the 11 autopsy specimens from patients who died between 1951 and 1956 and who were not studied clinically by us. The incidence and severity of the renal lesions was somewhat more severe in the group studied by us. Our patients were studied more closely, were treated more intensively, and lived longer than the 11 pa-



FIG. 26 Patient #3 Autopsy January 1956 Chronic lupus glomerulonephritis and superimposed pyelonephritis. Section of kidney. Note that the cortex is narrow. The radial pattern of the pyramids is abnormally prominent. Small interstitial abscesses can be seen at the upper and lower poles.

tients in the post mortem group 1951-1956. Therefore the increased severity of the renal lesions in the group of patients studied by us may be related to prolongation of life.

E. The renal lesions in cases of subacute glomerulonephritis studied postmortem

Because of the morphologic resemblance of the lesions of the advanced stages of lupus nephritis to those of the common type of glomerulonephritis, a comparative analysis was made of the histologic features in the two diseases. In Table V are set out the histologic findings in the kidneys of 15 autopsy cases of subacute glomerulonephritis. These were consecutive cases in the period 1952-1955 taken from the files of the Department of Pathology. In all the clinical and pathologic features were considered to be typical of subacute glomerulonephritis and in none was there clinical or pathologic evidence of SLE.

A comparison of these findings (Table V) with those of the autopsy cases of lupus nephritis (Tables VII and IX) revealed that although many features were common to both diseases there were also many differences (Table XI). Certain features considered characteristic of lupus nephritis such as local necrosis, karyorrhexis, hematocytin bodies and hyaline thrombi did not occur or were very rarely seen in subacute glomerulonephritis. Wire loop lesions and fibrinoid degeneration were far less commonly found than in lupus nephritis. Mild degrees of glomerular hypercellularity were common in lupus nephritis but

TABLE V

*In analysis of the nature and severity of the renal lesions in 15 autopsy specimens from patients with subacute glomerulonephritis**

Histologic Features Analyzed	Grades of Damage				Total Number Abnormal
	4+	3+	2+	1+	
Glomeruli					
Basement membrane thickening	1	3	1	6	11
Wire loop' lesions	0	0	1	2	3
Fibrinoid	0	1	0	1	2
Hypocellularity	2	10	1	2	15
Local necrosis	0	0	1	0	1
Karyorrhexis	0	0	1	0	1
Hematoxylin' bodies	0	0	0	0	0
'Hyaline' thrombi	0	0	0	1	1
Capsular adhesions	5	5	2	3	15
Crescents	4	5	1	0	10
Ischemia	0	10	2	3	15
Protein in Bowman's space	0	0	1	3	4
Total glomerular damage	8	4	3	0	15
Tubules					
Degeneration	0	15	0	0	15
Atrophy	0	3	9	3	14
Dilatation	0	3	4	5	12
Protein in tubular lumina	0	7	7	1	15
Cast in tubular lumina	0	3	10	1	14
Total tubular damage	2	13	0	0	15
Interstitial tissue					
Edema	0	1	9	9	15
Fibrosis	0	3	10	2	15
Inflammation	0	2	9	3	14
Arteries					
Scleroses	0	0	0	9	9
Filumoid	0	0	0	1	1

* Cases studied from the files of the Department of Pathology, University of Illinois, 19, 2, 1955.

the incidence and severity of this feature were definitely greater in subacute glomerulonephritis. Fibroepithelial crescents and glomerulocapsular adhesions were more common in subacute glomerulonephritis.

Tubular damage was definitely more severe in subacute glomerulonephritis. This was especially true of atrophy and dilatation, and pointed to a more chronic disease process. This interpretation was confirmed by the higher incidence and greater severity of interstitial fibrosis among the cases of subacute glomerulo-

TABLE XI

1 comparison of the incidence of histologic abnormalities in biopsy and autopsy specimens of lupus nephritis, with autopsy specimens of glomerulonephritis

Histologic Features Analyzed	Percentage Incidence of Abnormalities in			
	Lupus nephritis			Glomerulo nephritis
	40 biopsy specimens*	9 autopsy specimens†	20 autopsy specimens‡	15 autopsy specimens§
Glomeruli				
Basement membrane thickening	100	100	100	73
'Wire loop' lesions	74	100	60	20
Fibrinoid	77	89	45	13
Hypercellularity	74	100	90	100
Local necrosis	34	56	30	7
Karyorrhexis	28	78	35	7
Hematoxylin" bodies	10	33	25	0
Hyaline" thrombi	0	33	30	7
Capsular adhesions	41	78	55	100
Crescents	8	33	40	67
Ischemia	95	100	95	100
Protein in Bowman's space	75	78	35	27
Tubules				
Degeneration	93	100	90	100
Atrophy	56	78	85	93
Dilatation	60	44	50	80
Protein in tubular lumina	97	100	100	100
Casts in tubular lumina	58	89	65	93
Interstitial tissue				
Edema	49	100	75	100
Fibrosis	70	89	75	100
Inflammation	58	89	80	93
Arteries				
Sclerosis	63	67	55	60
Fibrinoid	44	67	■	7

* See Table VII A

† See Table VII B

‡ See Table IX

§ See Table X

nephritis Fibrinoid changes in the arteries were definitely more common in the cases with lupus nephritis, while the incidence of sclerotic changes was similar in the two series

F Evolution of the renal lesions of lupus nephritis

(1) Analysis of the findings—

In 21 patients two or more specimens were studied by biopsy or autopsy at intervals varying between six weeks and sixteen months. Seven of these patients died, and the analysis of their autopsy studies is included in this discussion

In most cases the interval between studies was four to eight months. Two specimens were studied from each of twelve patients, three specimens from each of seven patients, and four and five specimens from one patient each. The shortest period between the first and last histologic study was six weeks (#27), the longest was 23 months (#31).

The first biopsy was normal in six patients. In four (#3, 5, 7, 8) the second or third biopsies taken at intervals up to 22 months remained normal. In the other two (#6, 11) repeat studies disclosed the development of a mild to moderate membranous glomerulonephritis in four and fourteen months respectively. Glomerulitis was found in the first biopsy of seven patients. In one (#16) the lesion was unchanged one year later. Slight progression of the lesion occurred in two patients (#12, 14) in fifteen and four months respectively. In four cases (#13, 18, 19, 21) the lesion progressed from glomerulitis to glomerulonephritis during a period of observation ranging from four to ten months.

Glomerulonephritis was observed in the first biopsy in eight instances. In one (#29) there was slight progression in the first three months but subsequently the changes had not progressed nine months later.* In seven (#22, 23, 25, 26, 27, 30, 31) considerable progression of the already severe renal lesion was observed in a period ranging from 6 weeks to 23 months.

(2) *Reconstruction of the histologic evolution of lupus nephritis*—

From our studies it is evident that the renal lesions of lupus nephritis once they had developed inevitably progressed. The morphologic appearance of the lesion changed with this progression. The serial pathologic specimens available in this study have permitted an accurate reconstruction of the histologic evolution of lupus nephritis from the earliest to the most advanced stages.

The earliest and milder lesions of lupus nephritis were confined to the glomeruli. At this stage an irregular focal thickening of the basement membrane in small areas at the periphery of the tuft was frequently found. It has a somewhat smudgy appearance. Although strongly suggestive of fibrinoid this appearance could not definitely be attributed to deposition of fibrinoid as the PAS and Mallory stains did not usually give the characteristic staining reactions. In almost all instances a mild local proliferation of endothelial cells was noted in association with the thickening of the basement membrane. This usually appeared to be due in part at least to clumping of cells, the result of narrowing and of conglutination of capillary loops. In some cases a diffuse proliferative glomerulitis was noted. This suggested that the areas of local hypercellularity were not due only to clumping of cells but that there was true local proliferation of endothelial cells. The importance of these early glomerular lesions of lupus nephritis has not been emphasized except by Steckney and Keith (272, 274) and in Smith's recent study (261). Moreover they have detected and we have confirmed that these lesions are present in autopsy specimens side by side with more advanced and typical changes. They probably represent glomeruli recently affected in a fresh exacerbation of SLE.

* This patient has since been restudied twelve months later. No further progression of the renal lesion has occurred.

Some cases of glomerulitis progressed slowly during the period of observation. In many cases the local and focal glomerulitis progressed gradually and the following features more peculiar to lupus nephritis appeared: the narrowing and conglutination of capillary loops became more marked in local areas and the local necrotic lesions developed within these lesions karyorrhectic hematoxylin bodies fibrinoid changes and occasional hyaline thrombi were observed. In other cases the local hypercellularity was less obvious as thickening and fibrinoid changes of the glomerular basement membrane became the predominant feature. At first this was observed at the periphery of the glomerulus later areas throughout the glomerulus were involved. Wire loop lesions were noted at this stage. This was the membranous form of lupus nephritis which was found either alone or in combination with local necrosis.

Frequently in the areas of local necrosis the glomerulus became adherent to Bowman's capsule. The local adhesions gradually underwent organization and eventually became fibrotic. When adhesions between the altered glomerular tuft and Bowman's capsule were more extensive proliferation of epithelial cells was observed and epithelial crescents and later fibroepithelial crescents were formed. At this stage which we have called subacute lupus glomerulonephritis the histologic features peculiar to lupus nephritis were less prominent in some cases but were still present. Evolution to chronic glomerulonephritis with fibrosis and hyalinization of many glomeruli was uncommon in both biopsy and autopsy specimens.

In the early stages no tubular vascular or interstitial tissue changes were observed. As the glomerular lesions became more pronounced tubular degenerative changes appeared: the interstitial tissue became edematous at first in focal areas and later throughout the sections. Interstitial fibrosis was observed later than interstitial edema in the course of the disease. Small interstitial infiltrates of chronic inflammatory cells began to appear with the development of interstitial edema and fibrosis. Initially foci of inflammatory cells were often located around the glomeruli only later were they observed in other areas of the cortex and medulla. A superimposed pyelonephritis was observed in the subacute and chronic glomerulonephritic stages in three instances. Vascular changes occurred only late in the disease. Fibrinoid changes were observed in the walls of small arteries and arterioles in some cases these preceded the appearance of mild sclerosis.

The rapidity of evolution of the renal changes in lupus nephritis varied greatly from case to case. In our opinion the presence of severe fibrinoid changes local necrosis hematoxylin bodies and hyaline thrombi must be considered as evidence of marked activity of the lupus nephritis they were observed more commonly and were more severe during acute clinical exacerbations of SLE.

3 THE RELATIONSHIP OF STRUCTURAL CHANGES IN THE KIDNEY TO RENAL FUNCTION

Addis introduced quantitative examination of the urinary sediment as an indirect means of observing the nature and extent of lesions affecting the kidney.

TABLE VII

Results of urinalyses made just prior to histologic study (67 studies made)

Lesion	Kidney							Total
	Glomerulitis			Glomerulonephritis				
	Normal	Membranous	Membranous and proliferative	Membranous	Membranous and proliferative	Subacute	Chronic	
Normal	12	4	3	0	0	0	0	19
Slight excess RBC only (3-12/HPF)	1	1	0	0	0	0	0	2
Slight excess WBC only (5-15/HPF)	1	0	0	0	2	0	0	3
Slight excess RBC and WBC	1	1	2	0	0	0	0	4
Excess WBC (5-15 HPF) No borate number of casts	2*	0	2	2	1	0	0	8
Excess RBC and moderate number of casts	0	0	2	1	1	1	0	5
Large number of casts with or without excess RBC and WBC	0	0	0	5	2	6	7	20
Totals	17	6	7	8	8	7	7	62†

* One patient (#3) had had attacks of pyelitis. The other (#10) had nephrosclerosis.
 † Includes all studies made just before death.

(1) However he recognized the diagnostic limitations of this method of study.
 (2) The technique of serial renal biopsies has offered us a unique opportunity to study directly the nature and extent of lesions affecting the kidney and to compare and relate the pathology to the findings on urinalysis and to renal function assessed at the time of biopsy. These interrelationships will be discussed primarily from the point of view of the status of the urine and of renal function.

1. Microscopic urinalysis

(1) Normal urinalysis—

From Table VII it will be noted that the microscopic analysis of the urinary sediment was normal 19 times. In twelve instances the kidneys were histologically normal and in seven there was mild lupus nephritis (glomerulitis). In two patients (#6, 11) urinalysis and the renal histology were normal at the time of the first study; subsequently both developed membranous glomerulonephritis and leucocytes and moderate numbers of casts were found in their urine. Four patients (#12, 18, 19, 21) had glomerulitis when first studied but no abnormality was found on microscopic urinalysis. When studied later three of these patients had developed glomerulonephritis and the urinalysis had become abnormal in all four.

(2) Abnormal urinalysis—

On 43 occasions the urinalysis was abnormal (Table VII). In nine (21%)

nations there was a slight excess of leucocytes or erythrocytes or of both in the urine but not more than occasional hyaline or granular casts were found. The kidneys of three of these patients were normal but when one (#11) subsequently developed a local and generalized membranous glomerulonephritis the urinalysis had become abnormal. One patient in this group (#13) had four biopsies there was only a slight change in the renal lesion which progressed from glomerulitis to mild glomerulonephritis but leucocytes and erythrocytes were the only abnormality found on microscopic examination of the urine.

On 14 occasions a moderate number of casts was found on examination of the urine. All these urines contained 5-15 leucocytes, and five had 3-12 erythrocytes per high power field. One of these patients (#3) had had acute pyelitis and another (#10) had benign nephrosclerosis neither had lupus nephritis. In two (#12-14) membranous and proliferative glomerulitis was found on each of two examinations. In one examination (#26) subacute glomerulonephritis was found membranous or proliferative and membranous glomerulonephritis was diagnosed in the other seven biopsies.

On twenty occasions in eleven patients large numbers of casts were found in the urinary sediment. All these patients had lupus glomerulonephritis membranous in five membranous and proliferative in two subacute in six and chronic glomerulonephritis in seven. Nine of the eleven patients had nephrotic or pseudo nephrotic syndrome due to lupus nephritis. All had excess numbers of erythrocytes in the urinary sediment and on nine occasions there were 40 or more erythrocytes per high power field. There were less than 5 leucocytes per high power field in six cases, 5-15 in ten cases and more than 10 leucocytes per high power field in four cases. Hyaline and granular casts were each found on nineteen occasions, cellular casts (leucocyte or epithelial) on thirteen, erythrocyte casts on four occasions and fatty casts or oval fat bodies on fourteen occasions. Fatty casts and oval fat bodies were found on thirteen out of seventeen examinations in patients who had nephrotic and pseudonephrotic syndrome and in one patient (#33) who had chronic lupus glomerulonephritis.

On 21 occasions an increased number of leucocytes was found in urines which contained no casts or a moderate number of casts. In many of these urines the leucocytes were clumped and in a few, leucocyte casts were found. This finding was reminiscent of the urine in pyelonephritis and in patients with clumps of leucocytes in the urine the diagnosis of lupus nephritis must be considered (78). Organisms were cultured from the urine of many of these patients but from one biopsy specimen only. In only one patient (#3) was there clinical or histologic evidence of pyelitis or pyelonephritis. Others developed evidence of infection later in the course of their disease when their kidneys were severely involved by lupus nephritis.

As we are dealing with a single disease we can compare the relationship of abnormalities in the urinary sediment to the degree of histologic changes in the kidney. From a study of Table XII it is clear that urinalysis is of value in assessing the extent of the renal involvement in lupus nephritis. In the fifteen

Two other patients had no evidence of lupus nephritis. One (#3) had had attacks of pyelitis the other (#10) had nephrosclerosis. These cases are excluded from this analysis.

instances with normal kidneys microscopic examination of the urine was normal in twelve and in three there was only a slight increase of leucocytes erythrocytes or both. Fifteen cases were diagnosed histologically as mild lupus nephritis (glomerulitis). Urinalysis was normal in seven there were slight abnormalities but no casts in four and there were a moderate number of casts in four cases. Thus in most cases with renal involvement confined to the glomeruli there were no casts in the urine and in none of these cases was there a large number of casts.

In 30 instances biopsy sections were interpreted as consistent with lupus glomerulonephritis. In all but two instances casts were found in the urine and were present in large numbers in twenty. The presence of many casts in the urine was a definite indication of glomerulonephritis—thatis of structural damage to both glomeruli and tubules.

B Proteinuria

The amount of protein in the urine was measured either semiquantitatively (0 to 4+) on an early morning specimen of urine or quantitatively on a 24 hour urine specimen. Histologic observations on the presence or absence of proteinaceous material in Bowman's spaces and tubules were made in all cases and these are summarized in Table VIII. In thirty eight instances the patient had proteinuria at the time of the biopsy. Proteinaceous material was observed in the tubules of eleven in Bowman's spaces only in one case and in Bowman's spaces and tubules of the remaining twenty six. In nineteen instances the patient did not have proteinuria when the biopsy was done. Proteinaceous material was found in Bowman's spaces and tubules in ten and in the tubules only in six. Protein was not found in either Bowman's spaces or tubules in only three patients. The presence of proteinaceous material in Bowman's spaces and tubules of patients who have no measurable proteinuria constitutes additional evidence for the view that protein is normally filtered by the glomerulus and is absorbed by the tubules (2, 135).

Proteinuria is a common finding in those conditions in which the glomerular basement membrane is thickened. For this reason an analysis was made not only of the total glomerular damage but also of the changes in cellularity of the glomerulus and in the thickness of its basement membrane. The relationship between on the one hand proteinuria expressed quantitatively or semiquantitatively and on the other hand kidney damage, glomerular damage, hyper-

TABLE VIII

Relation of proteinuria to the presence of proteinaceous material in Bowman's space and in renal tubular lining in 57 biopsy specimens

Proteinuria	Protein in Both Bowman's Space and Tubular Lumen	Protein in Bowman's Space Only	Protein in Tubular Lumen Only	No Protein Seen in Bowman's Space Or Tubular Lumen	Total
Present	26	1	11	0	38
Absent	10	11	6	3	19

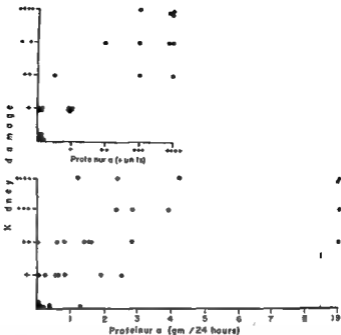


FIG 27 (a)

FIG 27 The relationship between the degree of proteinuria and the degree of (a) total kidney damage (b) glomerular basement membrane thickening (c) hypercellularity of the glomerulus and (d) tubular damage in patients ill with SLE who were studied by renal biopsy. The amount of protein in the urine is expressed either in plus units or in grams per 24 hours. Note that there is good correlation between the amount of protein in the urine and total kidney damage, thickening of the glomerular basement membrane and tubular damage. There is poor correlation between the amount of protein in the urine and glomerular hypercellularity.

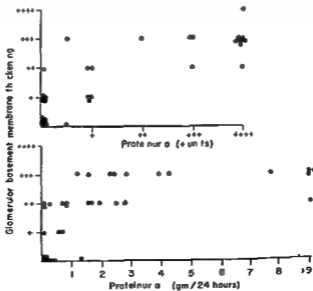


FIG 27 (b)

cellularity of the glomerulus, thickening of its basement membrane, and tubular changes, is shown in Figure 27. Study of the charts indicates that there was no correlation between hypercellularity of the glomerulus and proteinuria. There was good correlation between the total kidney damage, glomerular damage or tubular damage and the amount of protein in the urine. And there was obvious

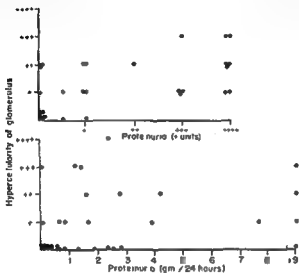


FIG 27 (c)

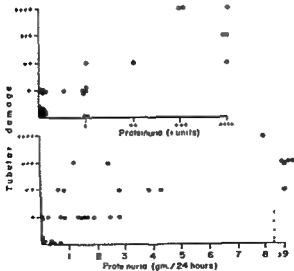


FIG 27 (d)

correlation between the changes in the glomerular basement membrane and the quantity of protein in the urine

C Tests of renal function

In their study of hypertensive patients before and after sympathectomy Talbott and his colleagues first demonstrated the value of studying the relationship between renal function and renal structure in the living patient. Their studies were made using renal tissue removed at operation (281). The advent of a technique for percutaneous biopsy of the kidney has immeasurably widened the scope of such studies.

Our patients have been studied over periods of time up to two years. Studies of renal function were made just before each biopsy was taken and, in those who died within a few weeks of death. Frequently studies were also made at varying intervals between biopsies. During the two years of the study serial changes in the clinical and laboratory data were observed and compared with the histology on five and four occasions in cases #23 and 13 respectively, on three occasions in cases #6, 7, 11, 12, 22, 29, and 31, and on two occasions in twelve other cases. Examples of these changes as observed serially are given in Figures 7 and 10.

The methods used for the renal function studies and for the semi-quantitative assessment of histologic changes are described in Section V. For each biopsy the appropriate function was compared with the degree of overall kidney damage, with the degree of glomerular damage, and with that of tubular damage. Degrees of structural change were plotted on the ordinates of the graphs, the function test on the abscissa.

(1) Biochemistry of the blood—

The blood creatinine level was measured on 59 occasions at the time of the renal biopsy (Fig. 28). It was 1.4 mg/100 ml or less in all sixteen cases with normal kidneys; in sixteen of the seventeen cases in which kidney damage was estimated as 1+; and in seven of the ten cases in which the damage was 2+.

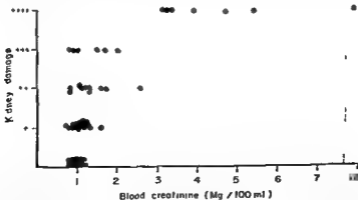


FIG. 28. The relationship between the blood creatinine levels and the degree of kidney damage in patients ill with SLE who were studied by renal biopsy (see text).

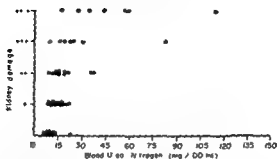


FIG. 29 The relationship between the blood urea nitrogen levels and the degree of kidney damage in patients ill with SLE who were studied by renal biopsy (see text).

two the level was 16 and 17 mg/100 ml and in the third (#23 biopsy #1) the creatinine level was 2.6 mg/100 ml despite the fact that the histologic change was not gross. She was ill with the nephrotic syndrome and there was considerable edema of the interstitial tissue of the kidney. Moderate elevation of the blood creatinine levels has been observed in other patients with nephrotic syndrome—whatever the underlying pathology. In these patients when the edema of the interstitial tissue has decreased after diuresis the creatinine levels have fallen toward normal. The creatinine level was less than 1.4 mg/100 ml in three of six cases in which there was 3+ renal damage and between 1.4 and 2.0 mg/100 ml in the remaining three. It was greater than 3.0 mg/100 ml in all nine cases with 4+ renal damage. Thus the blood creatinine level remained within normal limits until the kidneys were severely damaged and a raised creatinine level reflected only severe degrees of kidney damage.

The blood urea nitrogen was measured on 56 occasions (Fig. 29). The level of the BUN was 14 mg/100 ml or less in fifteen of the sixteen cases with normal kidneys, in ten of seventeen cases in whom the renal damage was estimated at 1+ in four of eleven cases with 2+ renal-structural damage and in one case with 3+ damage. The level was between 15 and 30 mg/100 ml in one case with normal kidneys, in seven with 1+ structural change, in five with 2+ damage and in five with more severe changes. BUN levels of more than 30 mg/100 ml were encountered twice in patients with 2+ damage and in seven cases where the lesion was more advanced.

The blood non-protein nitrogen was measured on 63 occasions (Fig. 30). The level of the NPN was 35 mg/100 ml or less in fifteen of the sixteen cases with normal kidneys, in only eight of the fourteen cases in whom the renal damage was estimated at 1+ and in seven of fifteen cases in whom it was 2+. In twelve cases with 1+ or 2+ renal damage the NPN level was in the range 2.5-5.0 mg/100 ml and in two it was 6.0 mg/100 ml. In only two of the eighteen instances in which the renal pathology was 3+ or 4+ was the NPN less than 35 mg/100 ml.

Thus when the kidneys were histologically normal the level of serum creatinine was within normal limits in all cases and the levels of BUN and NPN in all

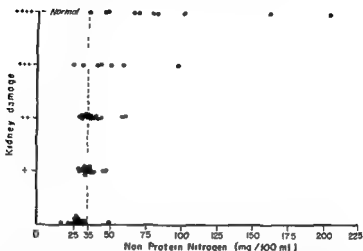


FIG. 30 The relationship between the blood non protein nitrogen levels and the degree of kidney damage in patients ill with SLE who were studied by renal biopsy (see text)

but one instance. With slight to moderate structural damage (1+ to 2+) the levels of BUN and NPN were raised slightly above the normal of 14 mg/100 ml and 35 mg/100 ml respectively in 43% and 41% of cases, and were considerably above normal values in 7% of cases. By contrast the level of creatinine was raised slightly above the normal of 1.4 mg/100 ml in only 11% of cases with slight to moderate structural damage, and was considerably elevated in 4%. Thus with slight to moderate structural damage the BUN and NPN were perhaps more sensitive indicators of the change in renal function than was the creatinine, on the other hand both BUN and NPN are subject to greater variation as a result of extrarenal factors such as dehydration and variations in the protein intake. When the renal damage was more advanced (3+ to 4+) little difference was observed in the proportion of cases with elevated blood creatinine, BUN or NPN levels.

As was expected the levels of urea nitrogen, non-protein nitrogen, and of creatinine in the blood did not reflect accurately the degree of underlying renal structural damage glomerular, tubular or both. They were raised only when the damage was severe, and were not sensitive indices of loss of renal function.

(2) Specific tests of renal function—

Specific gravity concentration tests were done within a few days of the renal biopsy on 43 occasions. The results are shown in Figure 31. In general as the renal damage became more severe, the concentrating power of the kidney decreased, and this was found to be equally true when relationships with glomerular damage or tubular damage were assessed independently. The figure 1.022 was taken as the lower limit of the concentrating power of the normal kidney. The concentrating power was 1.022 or greater in nine of twelve cases with normal kidneys, in twelve of fourteen cases with 1+ kidney damage, and in four of seven cases with 2+ damage. It was 1.020 in three cases with normal kidneys and in two with 1+ damage, and 1.018 to 1.020 in three with 2+ damage.

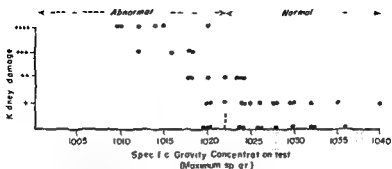


Fig. 31 The relationship between the maximum urinary specific gravity and the degree of kidney damage in patients ill with SLE who were studied by renal biopsy (see text)

In all ten cases in whom there was 3+ to 4+ damage the maximum specific gravity of the urine was less than 1020 and it was 1010 or less in five of the six cases with 4+ damage.

Urea clearances were made in all instances (Fig. 32) and the results were expressed as a percentage of average normal renal function (ANRF). The normal clearance was assumed to be 70% or more. From Figure 32 it is seen that there was a close correlation between the urea clearance and the degree of renal damage. Values of 70% or greater were found in eighteen instances with normal kidneys or 1+ damage, in two with 2+ damage, and in none where the damage was more severe. Values of 50% to 70% ANRF were found in two instances with normal kidneys, in eight with 1+ damage, in three with 2+ damage, and in one with a more advanced lesion. Values less than 50% were not found until there was 2+ damage (five occasions) and were observed in twelve of the thirteen cases with more advanced lesions. Thus the urea clearance test gave a fairly accurate estimate of the degree of overall damage to the kidney as related histologically. Similar results were obtained when glomerular damage and tubular damage were assessed independently.

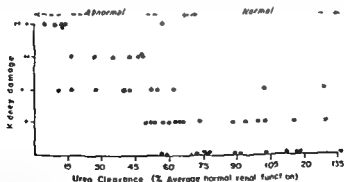


Fig. 32 The relationship between the urea clearance (expressed as a percentage of average normal renal function) and the degree of kidney damage in patients ill with SLE who were studied by renal biopsy (see text)

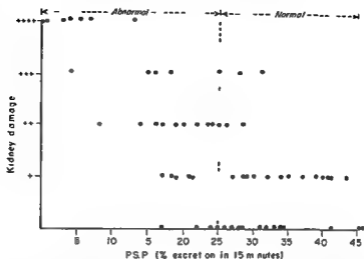


FIG. 33 The relationship between the amount of phenolsulphonphthalein excreted in fifteen minutes and the degree of kidney damage in patients ill with SLE who were studied by renal biopsy (see text)

The excretion of phenolsulphonphthalein was measured fifteen minutes after intravenous injection. The results of 59 studies are set out in Figure 33. Twenty-five per cent or more was excreted in 26 of 34 cases with normal kidneys or 1+ damage, in three of eleven with 2+ damage, in three of seven where the damage was 3+, and in none where it was 4+. It was between 15% and 25% in fourteen of the remaining seventeen in whom renal damage was 1+ to 3+. In all seven cases with 4+ damage the excretion of PSP was less than 15% in 15 minutes and in six was below 8%. Thus the 15 minute excretion of PSP gave an accurate estimate of the degree of renal damage.

Conclusion In Table XIV the renal damage, estimated histologically, has been compared with the results of the specific gravity concentration, urea

TABLE XIV

The relationship between the degree of histologic damage and the number of abnormalities found when patients with SLE were studied by means of three simple tests of renal function

Renal Damage	Number of Cases*	All Three Tests Normal	One of Three Tests Abnormal				Two of Three Tests Abnormal			All Three Tests Abnormal
			Urea clear	Sp gr conc	PSP	Total	Urea clear P ₅₀	Sp gr conc P ₅₀	Total	
0	14	8	2	2	1	5	1	0	1	0
+	13	5	3	1	2	6	1	1	1	1
++	9	0	2	0	2	4	1	1	1	3
+++	11	0	0	0	0	11	1	2	3	3
++++	11	0	0	11	11	0	0	0	11	6

* Only cases in which all three tests were made are included in this table

clearance, and phenosulphonphthalein excretion tests. It can be seen that when the kidneys were normal histologically, all three tests of renal function were normal in eight of the fourteen examinations; that one test only was abnormal on five occasions; and that both the urea clearance and P-S-P excretion were low on one occasion. It should be emphasized that although tests of function were abnormal in six instances the degree of diminution in function was slight. In cases with minimal histologic changes in the kidney (1+) all three tests of function were normal in five of the thirteen examinations; and all three were abnormal in only one. Again the degree of diminution of function was slight in respect of each test.

With a moderate degree of kidney damage (2+) there was no instance in which all three tests were normal. One was abnormal on four occasions; two were abnormal on two occasions; and all three were abnormal three times. Of the six instances in which the kidney damage was estimated as 3+ two tests were abnormal on three occasions; and three tests were abnormal on the other three. With the most severe damage (4+) all three tests were abnormal on all six occasions.

It has been shown above that the specific gravity, concentration, urea clearance, and P-S-P tests each reflected the underlying degree of kidney damage. Nevertheless for each test there is a considerable biologic and experimental variation. From Table XIV it is observed that any one of these three tests may be abnormal when the kidneys were histologically normal; but that the degree of abnormality was slight. In assessing the degree of kidney damage it is also seen that no single test was superior to the other two. But a combination of all three tests gave an excellent overall impression of the underlying damage—a better assessment, in fact, than when any one of the tests was used alone. When the functional impairment was estimated by an assessment of all three simple tests taken together an accurate impression of the nature of histologic damage was obtained.

VII THE CLINICOPATHOLOGIC FEATURES OF LUPUS NEPHRITIS

I THE INCIDENCE OF LUPUS NEPHRITIS IN PATIENTS WITH CLINICALLY DIAGNOSED SLE

The criteria used by different investigators for the assessment of renal involvement in SLE are so variable that it is difficult to compare one study with another. Many reports are based on abnormal urinary findings, and interpretation of their data must depend on whether the proteinuria and cylindruria were permanent or whether they appeared temporarily during exacerbations of SLE. This consideration applies to the series reported by Jessurajamont-Hayes and Ragin (127). These authors found abnormal urinary sediments in 61% of their series of 44 cases and in 56% of the 279 cases reviewed by them. Montgomery more accurately diagnosed renal involvement by the presence of *per-*

phrit
The

1938 and 1947 (191) Using these criteria 64% of the second series had evidence of renal involvement but only 13% of the first series. It is difficult to account for this discrepancy. It will be noted that the second series antedates the use of cortisone and corticotrophin therapy. Thus increased longevity as a result of successful steroid therapy cannot explain the increased incidence of lupus nephritis from 1938 to 1947. These patients may have lived longer because of treatment with transfusions, blood plasma, sulfonamides and penicillin. In Harvey's series only 26 per cent of 138 patients had no signs of renal involvement. Thus there was some evidence of affection of the kidney in 74% of his patients.

The 33 patients reported here have not been followed for as long a time as those observed by Montgomery (190-191), Jessar (127) or Harvey (110). Despite this 24 of 33 patients had renal involvement on histologic evidence (i.e. 73%). Using the criteria of Montgomery, 21 patients have had *persistent proteinuria or cylinduria* due to lupus nephritis (i.e. 64%) in one additional case (#10) persistent proteinuria and cylinduria were the result of benign nephrosclerosis.

As our clinical interests have covered the field of diseases of the kidney as well as that of SLE we considered it possible that our selection of cases may have been biased in favor of cases of SLE with renal involvement. However it will be observed that the incidence of renal involvement in our patients was similar to that in other large series in which this bias did not exist. Harvey and his colleagues (110) have also observed that structural damage to the kidney by SLE is more common than urinary findings and tests of renal function would have led them to believe.

The assessment of renal involvement from post mortem material has been subject to considerable error for there are few studies in which the particular orientation of the authors has not played a part in the selection of their material. Ten of our patients died and post mortem examinations were made on the kidneys of nine. All had a glomerulonephritis. These results are comparable with others. For example Mook and his colleagues (193) examined the kidneys of 22 patients who died with SLE and found evidence of kidney involvement in all. Baehr (9) found glomerular lesions in 78% of 23 post mortem examinations and Harvey (110) found some degree of involvement of the kidneys by SLE in 89% of 38 cases.

We may therefore conclude that the kidney is involved by SLE in a high proportion of patients. On clinical grounds about two thirds to three quarters of patients with SLE have lupus nephritis and on pathologic grounds an even higher proportion show evidence of kidney involvement.

2 THE TIME OF ONSET OF LUPUS NEPHRITIS

The time of appearance of the first significant symptom has been taken as the time of onset of the disease. In some cases a single sign or symptom (e.g. Raynaud's phenomenon, polyarthralgia, biologic false positive test for syphilis) occupied the stage for a long period of time and the duration of the disease

was interpreted in this light. In four patients (#24, 27, 30, 32) edema was the presenting symptom and made its appearance at the time of or shortly after the onset of other symptoms of SLE. Seven other patients (#22, 23, 25, 28, 29, 31, 33) presented to us with renal symptoms. However, all of these patients had had other symptoms or signs of SLE for from two to ten or more years. When first seen, all of these eleven patients had severe lupus nephritis (glomerulonephritis).

By contrast, in eleven patients renal involvement was initially discovered by urinalysis, by tests of renal function or by renal biopsy (#12-21 and #26). All had come to hospital primarily because of non renal manifestations of SLE. Only one of these patients had severe lupus nephritis when first studied (#26), and she died a few months later. Symptoms of SLE had been manifest for periods of from three months to eleven years in this group of patients. Eleven patients (#1-11) had no evidence of renal affection by SLE after periods of time which covered from 11 months to 9½ years. Two of these patients (#6, 11) subsequently developed lupus nephritis 17 months after the onset of their disease. We agree, therefore, with Hamburger and his colleagues (107) that the time of appearance of renal affection by SLE is variable: the kidney may become involved at the onset of the disease or at any time thereafter until just before death.

3 THE CLINICAL FEATURES OF LUPUS NEPHRITIS

Mild lupus nephritis. Ten patients had mild lupus nephritis when first seen. The glomeruli were affected but there was no significant involvement of the tubules. In none of these patients were renal manifestations a prominent feature of the clinical picture. In three no abnormalities were found in the urine, two excreted excess amounts of protein but no cells or formed elements, two had a slight excess number of erythrocytes, two excreted excess protein and white cells, and in only one patient were there casts in the urine in addition to protein and cells. There was a very slight increase of the blood NPN in two and a slight decrease in renal function in one. Three had persistently elevated blood pressures. In two hypertension appeared only during exacerbations of SLE. Thus in the early stages of renal involvement there was little to be found on clinical and laboratory examination.

Eight of these 10 patients with mild lupus nephritis have been studied serially by renal biopsy, and four have developed evidence—both clinical and pathologic—of progression of their renal lesion. None has yet died. In none of these eight patients has there been any definite relationship between the frequency and severity of the exacerbations of SLE and the progression of their renal lesions.

Severe lupus nephritis. Twelve patients had severe lupus nephritis when first seen and their kidney lesions were classified as glomerulonephritis. By contrast with the ten patients with mild lupus nephritis, renal manifestations were a prominent feature of the clinical picture, and in some cases they were the dominant feature. Nine of the patients had nephrotic syndrome.

In all twelve patients definite abnormalities were found when the urine was first examined. Proteinuria was found in all, eleven had erythrocytes in the urinary sediment and these were present in large numbers in four, leucocytes were seen in the sediment of all but two and large numbers of casts were all observed in the urine of all patients. Nine had azotemia and in two the NPN was at the upper limit of normal. Renal function was decreased in nine and at the lower limit of normal in three. Eight of these patients have died, seven of them in uremia. The disease is progressing rapidly in two and more slowly in the other two. Five patients in this group had hypertension, but in two it developed only within three months of death.

Chronic lupus glomerulonephritis. This has been an uncommon pathologic finding. The lesions in three (#23, 29, 31)—diagnosed histologically as subacute glomerulonephritis when first seen—progressed to chronic glomerulonephritis and contraction of the kidney. In addition to these three patients #33 had chronic glomerulonephritis when first studied. The clinical course of these four patients progressed more slowly than that of those who died in the subacute stage of glomerulonephritis.

The blood pressure was permanently elevated above 150/90 mm Hg in seven patients. One (#10) a woman of 62 had nephrosclerosis but no evidence of lupus nephritis. Case #16 ill with glomerulitis was the only patient with mild lupus nephritis who had an elevated blood pressure. This may have been due to coincident essential hypertension. Another (#29) has had a blood pressure of 160/90 mm Hg for about two years. In the other four patients the blood pressure was raised for from two to twelve months before death in renal failure. Excluding the patient with nephrosclerosis the blood pressure was elevated in six (i.e. 18%). This incidence is slightly higher than that reported by others (110, 127). Hypertension was associated with advanced renal disease in four of the six patients and with moderately advanced renal disease in one. On the other hand the blood pressure was normal in four patients who died in uremia. These observations are similar to those of Harvey *et al.* (110).

4. NEPHROTIC AND PSEUDO NEPHROTIC SYNDROME

By the nephrotic syndrome we mean that clinical state—regardless of its cause—which is characterized by edema, massive proteinuria, hypoalbuminemia and hypercholesterolemia. The urinary sediment contains granular and hyaline casts and if they are carefully sought fatty casts and doubly refractile bodies are almost invariably found. Allen (4) whose definition of nephrotic syndrome is essentially similar to ours states: "It is well known that in a high percentage of cases of disseminated lupus erythematosus with clinically significant renal involvement (approximately 33%) nephrotic syndrome develops." Many authors have indeed mentioned the occurrence of nephrosis in SLE but the blood cholesterol values are often lacking in their reports and few have published all the essential data on their patients. We have been able to find but seven reports of cases of SLE in which all the above clinical criteria of the nephrotic syndrome are fulfilled. The first is the case of Brenner, Jeff and

Hochstein (35) reported in 1948. Two years later four cases were reported by Daugherty and Baggenstoss (63), another by Hamburger and his colleagues (107), and in 1953 Dubois reported a seventh (case #7) (66). In reports of several large series of patients we have been unable to find cases of the nephrotic syndrome with SLE. Jessar, Lamont Havers, and Ragan (127) reviewed 279 published cases of SLE and added 44 of their own. Although a number of these patients had proteinuria, hypoalbuminemia and edema there is no mention whether or not these findings were present in combination nor is there any reference to the levels of serum cholesterol. In an extensive review of the literature on SLE Ross and Wells (248) do not mention the nephrotic syndrome and Kushniruk (160) likewise did not observe it in his series of 75 cases of lupus erythematosus. Of the 138 cases of SLE recently reported by Harvey and his colleagues (110) only one (case #39) may have had the nephrotic syndrome and in this patient the cholesterol level was not recorded.

Much to our surprise seven of the 33 patients in our clinical study manifested all the criteria of the nephrotic syndrome at some time during the period of study. We have used serial renal biopsy as a tool in the study of the nephrotic syndrome (134-203) as well as in the study of the kidney affection in SLE. This very fact may explain the large proportion of cases with nephrotic syndrome in our series. An alternative explanation is more likely. Most reports of large series of cases of SLE with nephritis have been made by retrospective studies of post mortem material and hospital records which may have been incomplete. When we analyzed the available data on patients with SLE who died in our hospitals prior to 1952 we found that for our purposes adequate clinical and biochemical observations had not been recorded during the course of the patient's illness. There were several such cases which might have been diagnosed SLE with the nephrotic syndrome but in only one of them (G B) were the data adequate to diagnose nephrotic syndrome in retrospect.

In three of 33 patients in our clinical study all the criteria of the nephrotic syndrome were fulfilled *sic* that the serum cholesterol level was low or within the normal range (Table VI). These three patients were all acutely ill and in all three the clinical course was one of rapid progress to death; all three died within five months of the onset of edema. Because these patients were similar clinically we coined the term pseudo nephrotic (202) to describe the syndrome. Since these observations were made we have found a fourth case in our post mortem series (W O) who also had the pseudo nephrotic syndrome; she died within one month of the onset of edema.

Shearn and Pirofsky (259) called attention to a clinical variant of the nephrotic syndrome which occurred in patients ill with SLE. Three of their four patients had cholesterol levels within the normal range and a fourth patient had an im-

Sacks disease
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Stern and Pirofsky (259) called attention to a clinical variant of the nephrotic syndrome which occurred in patients ill with SLE. Three of their four patients had cholesterol levels within the normal range and a fourth patient had an initial Sacks disease had the fever was 120 mg/100 ml she died six months later.

In 1940 Keil (139) had written "Extreme hypercholesterolemia I have but

rarely observed in cases of systemic lupus erythematosus. In other instances the cholesterol value is normal or even diminished. The explanation of these low serum cholesterol levels is quite obscure. As in other patients with SLE the serum globulin level was raised and the thymol turbidity test was abnormal. The cephalin flocculation and prothrombin times were normal. The serum cholinesterase level was low (0.38 Δ pH units/hour) in the one patient in whom this observation was made. This contrasts with the abnormally high levels of serum cholinesterase usually found in the nephrotic syndrome (295). In three cases the liver was examined post mortem and no histologic damage was observed. It is nevertheless possible that SLE could produce some liver damage not detected histologically or by the limited tests of liver function performed in these patients. Such undetected liver damage might depress hepatic synthesis of cholesterol but as Gould has pointed out the plasma cholesterol level falls only with severe liver insufficiency and cholesterol synthesis may be increased in the presence of slight liver damage (100). Squire has noted that the more severe degrees of hypercholesterolemia in the nephrotic syndrome were associated with extremely low levels of serum albumin (271). No significant difference was noted between the serum albumin levels in the two groups of patients with nephrotic or pseudo nephrotic syndrome.

Careful analysis of the pathologic changes between the two groups revealed that the proliferative and basement membrane changes were of similar degree. However hyaline thrombi, wire loop lesions, karyorrhectic hematoxylin bodies and fibrinoid degeneration were observed more frequently and were more severe in the pseudo nephrotic than in the nephrotic group of patients. This morphologic difference is surely the expression of a more acute and severe involvement of the glomeruli of the patients ill with the pseudo nephrotic syndrome.

Cantarow and Trumper (44) state that a low plasma cholesterol level occurs in the terminal stages of a variety of diseases and that a fall from a previously elevated or normal level is of serious prognostic significance, particularly if associated with increasing nitrogen retention. It must be emphasized that in the pseudo nephrotic group the cholesterol levels were low *ab initio*. This low cholesterol level with other features of the nephrotic syndrome in a patient ill with SLE has in our experience implied a grave prognosis and rapid demise.

5. DISCUSSION OF PATHOLOGY

In the previous section the histologic features and evolution of lupus nephritis were set forth in detail. It remains now to discuss the significance of the lesions, their specificity and possible pathogenesis. Lupus nephritis is a disease which affects predominantly the glomerular capillaries and their constituent elements. In the earlier and milder stages of the disease the morphologic abnormalities are confined to the glomeruli, the tubules and interstitial tissue are involved later in the course of the disease. However in a few cases which clinically are severe at the outset the tubules and interstitial tissue may be involved from the beginning.

Clinically lupus nephritis does not run a protracted chronic course. This may be due to one or more of the following reasons:

1 The renal lesions progress more rapidly than those of most other renal diseases.

2 Exacerbations are more closely spaced.

3 Reversion to normal of glomerular lesions does not occur.

4 In many instances the systemic nature of SLE contributes to the death of the patient before the renal lesions have evolved to a more chronic and less active form.

Our studies indicate that the course and character of SLE and lupus nephritis may have changed during the past several years. There is no doubt that the life span of the patient has been prolonged by treatment, as a result renal changes tend to be more severe and chronic and less specific in character. Certain changes have been produced in the kidneys of experimental animals by the administration of cortisone (30, 340, 241, 287, 301) and it is possible that treatment with cortisone could produce similar changes in man. However the lesions seen in patients with lupus nephritis treated with cortisone are very different from those seen in the experimental animals and in the presumably normal kidneys of patients with *rheumatoid arthritis* treated for long periods of time with cortisone we have observed no abnormalities (230). Nevertheless it is conceivable that cortisone might modify the course and character of previously existing renal lesions and this treatment may have been a factor in lowering the incidence and decreasing the severity of certain changes such as wire loop lesions, fibrinoid and hematoxylin bodies. Unfortunately corticosteroid therapy does not prevent the progression of the renal disease.

Our study again emphasizes the pleomorphic nature of the renal lesions in SLE (3, 19, 151). Because they are so pleomorphic it is misleading to classify lupus nephritis as a variety of membranous glomerulonephritis (3, 4). An irregular local thickening of the glomerular basement membrane is the most consistent feature (19, 151) and varying degrees of thickening were found in all specimens studied by us. Nevertheless proliferative changes are common in the glomeruli and many other features are more typical of lupus nephritis than is thickening of the glomerular basement membrane.

Many observers have stated that wire loop lesions are one of the most characteristic features of lupus nephritis but they have been noted in many other renal diseases (3, 151, 231, 232). When they occur only in local areas at the periphery of the glomerulus and when they are associated with fibrinoid changes, wire loop lesions are more strongly suggestive of lupus nephritis. Moreover we wish to emphasize that wire loop lesions are not observed in the earliest stages and may disappear in the most advanced stages of the disease. When wire loops are present they are not diagnostic of lupus nephritis unless associated with other features more specific to this disease. On the other hand their absence does not exclude the diagnosis.

As reported by others fibrinoid changes were frequently observed in lupus nephritis. They were not universally present and in most instances especially

in the biopsy specimens, they were of mild to moderate severity. The relative scarcity of severe fibrinoid changes may be due to the fact that many biopsies were studied in an early or mild stage of the disease, and to the fact that most specimens were obtained during periods of relative clinical remission. Fibrinoid changes were more common and more severe when renal involvement was well established clinically, or when the biopsies had been taken from patients with acute exacerbations of SLE. The staining properties of fibrinoid suggested that it is closely related to but not identical with fibrin (7, 198-206). With the methods used in this study we could not detect any differences between glomerular and arterial fibrinoid—differences which have been suggested by recent studies (32, 192). In a few instances fibrinoid was noted along an essentially normal glomerular basement membrane. This strongly suggests the possibility that circulating protein material is deposited from the blood onto the membrane. It is not clear whether this deposition is related to the quantitative and qualitative changes in the serum proteins which occur in SLE.

The occurrence of local and focal glomerular necrosis has been reported by several investigators (19-151). Although Kemperer and his associates described this lesion in detail its importance and frequent occurrence were overlooked until Smith's recent study (264), its nature, however, is not well understood. Morphologically it is similar to the lesion of embolic glomerulonephritis described by Lohlem (172), and the possibility of an embolic etiology cannot be excluded entirely even in the absence of microorganisms in the blood and tissues. In none of the patients studied was a definite diagnosis of Libman-Sacks endocarditis made, moreover it is unlikely that the firm, verrucous vegetations of Libman-Sacks endocarditis could be responsible for embolic manifestations.⁴ Therefore it is probable that the glomerular necrotic lesions are primarily the result of local ischemia from occlusion of capillaries, basement membrane thickening, fibrinoid changes and endothelial cell proliferation. This lesion, which is unusual in other renal diseases with glomerular ischemia may be due to several factors including the rapidity of development of the capillary obstruction and the local release of abnormal substances peculiar to SLE (159).

Hematoxylin—or more accurately hematoxyphil⁵ (264)—bodies were found relatively infrequently in our material. This was probably a reflection of the high proportion of early lesions studied, and of the fact that only a limited number of glomeruli was available for study in each biopsy specimen. Nonetheless they were found in a few biopsy specimens in which the immediate fixation of the living tissue excludes the possibility that the formation of hematoxylin⁵ bodies results from agonal or postmortem changes. Their common occurrence in areas where pyknotic karyorrhexis and karyolysis are seen points to their probable origin from nuclear material and to their close relationship to the Har-

⁴ It is of interest that even in only one of the thirty⁶ of Gross (103) who found fixation of Jensen (127) and Harvey (110) each of whom observed this lesion in approximately one third of their patients. This difference in incidence is difficult to explain but the recent experience of other pathologists has been similar to ours (231-232).

grave's cell phenomenon (2), 104-109, 150, 162). It is not clear why hematoxylin bodies should be specific for SLE since for two cases (228, 306) one of which might have had SLE, they have not been observed in any other renal disease including those associated with necrotizing lesions of the glomeruli.

'Hyaline' thrombi in the glomerular capillaries are usually observed in the advanced and active stages of lupus nephritis but are not peculiar to lupus nephritis (128). They appear to consist primarily of fibrin and platelets. The mild to moderate basophilic staining which is observed in some instances may be due to the presence of material of nuclear origin and differentiation forms intraluminal 'hematoxylin' bodies may be difficult in the cases. 'Hyaline' thrombi must also be differentiated from eccentric fibrinoid thickening of the capillary wall—the so-called venereal capillitis (3). Their pathogenesis is obscure, we agree with Jones (128) that alterations in the lining cells of the capillaries and slowing down of the circulation probably play a role in their formation.

Clumping and proliferation of the endothelial cells of the glomerular tuft is common in lupus nephritis (19, 272, 274) as well as in many other renal diseases. In lupus nephritis this cellular proliferation usually affects small areas rather than the whole of the glomerular tuft and the degree of endothelial cell proliferation is not comparable in severity to that commonly seen in acute glomerulonephritis. Our findings suggest that endothelial cell proliferation follows the development of changes in the glomerular basement membrane. By contrast proliferation of epithelial cells and the formation of fibroepithelial crescents is a late manifestation of lupus nephritis. Thus in most cases of lupus nephritis proliferative changes are found in the glomeruli in addition to the membranous changes.

The lack of specificity and the difficulties of interpretation of the tubular changes in lupus nephritis have been discussed in the previous section. As in many renal diseases 'hyaline' droplets are observed in the cytoplasm of the convoluted tubular cells their reactivity with PAS is not as marked as in the kidney of amyloidosis and of multiple myelomatosis. The accumulation of 'hyaline' droplets is the result either of excessive reabsorption by or of altered metabolism of the tubular cells (211). Unfortunately it was impossible to carry out satisfactory mitochondrial stains on our material better to evaluate this process.

Fleming of the interstitial tissue of the kidney is a frequent finding. This correlates well with the swollen gross appearance of the kidney at autopsy, and with the frequent occurrence of nephrotic and pseudo-nephrotic syndrome. Interstitial fibrosis occurs even more commonly but is rarely sufficiently severe to cause gross contraction of the kidney.

With the exception of 'hematoxylin' bodies no other single histologic feature can be considered characteristic or pathognomonic of this disease. Nevertheless the histologic diagnosis is relatively easy in many cases as some histologic features occur frequently in a combination peculiar to lupus nephritis (e.g. 'wire loops', focal necrosis, fibrinoid and hematoxylin bodies). Accurate

histologic diagnosis is more difficult in the early stages before these lesions have developed. However, the local involvement of small areas at the periphery of the glomerulus by *membranous or membranous and proliferative changes* was found to be of great value in diagnosis in the early stages. Diagnosis is also more difficult in the late chronic stages when the typical lesions have become obscured by the chronicity of the process. Except for non-specific glomerulonephritis differential diagnosis does not present a serious problem. The histologic differentiation from other diseases which may simulate SLE clinically is discussed in section (X) below.

Although the systemic nature of the connective tissue changes in SLE is well known it is not clear whether involvement of the kidneys in SLE is a primary or a secondary manifestation of the disease. The kidneys are not always involved early in the disease but are affected ultimately in a very high proportion of patients. It is possible that renal involvement in SLE is a secondary manifestation such as a reaction to one or more abnormal circulating substances derived from either the connective tissue itself or from the reticuloendothelial system—both connective tissue changes and reticuloendothelial hyperplasia are known to occur in SLE. In our patients however the development of lupus nephritis was not specifically preceded by or related to any one or combination of clinical or laboratory abnormalities. Thus it seems more probable that lupus nephritis is a primary manifestation of the generalized involvement of the connective tissue.

VIII TREATMENT OF LUPUS NEPHRITIS

I GENERAL MEASURES

The treatment of SLE has been reviewed extensively in recent publications (55 67 110 267 269) and the therapeutic response of SLE to cortisone and corticotrophin is well known. We will therefore limit this discussion to certain aspects of the treatment of lupus nephritis.

The prevention and treatment of acute exacerbations of the disease are of prime importance. Intercurrent infections especially of the upper respiratory tract dental extractions (141) drug reactions (95 97) exposure to sunlight and other stimuli have been reported to precipitate acute exacerbations of the disease. One of our patients (#23) had an exacerbation of SLE a recurrence of nephrotic syndrome and an increase of hematuria following an upper respiratory tract infection. In another patient (#30) who was severely ill further deterioration of SLE and of lupus nephritis occurred after dental extraction. In two others (#21 31) the face rash became more prominent and the general symptoms and signs of SLE recurred after exposure to sunlight. In one of these patients there was an increase in the histologic damage to the kidney but this may have been coincidental. One patient (#18) who had many acute exacerbations and was not free from symptoms despite large doses of prednisone (30 60 mg daily) became acutely ill whenever she indulged in excessive physical exertion. All these precipitating factors must be avoided as far as possible. Exacerbations should be anticipated after infections and during and after preg-

TABLE V

Relationship of previous treatment with ACTH or Cortisone to the degree of kidney pathology found at the time of the first histologic study

ACTH or Cortisone Therapy Before First Study	Kidney Pathology at the Time of First Study			Total Cases
	Normal	Glomerulitis	Glomerulonephritis	
Yes	8	7	-	22
No	3	3	5	11

TABLE VI

Effect of treatment with ACTH and cortisone on the progression of renal lesions in 21 patients with SLE

Hormone Therapy between First and Last Histologic Study	Kidney Damage			
	Improved	Unchanged	Progressed +	Progressed ++
Yes	0	4	11	2
No	0	2	1	1

nancy. They must be treated vigorously and with a sense of urgency if and when they arise. Once clinical and histologic evidence of lupus nephritis had appeared, treatment was symptomatic.

1. The prevention of lupus nephritis

When the 33 patients in this series were first studied by us, 22 or 67% had histologic evidence of renal involvement compatible with SLE, and two others (#6-11) subsequently developed renal lesions of SLE. At present corticotrophin and

testosterone suppress the clinical manifestations, no effect of the steroids was demonstrable in preventing the development of lesions. We must conclude that there is at present no way in which the development of lupus nephritis can be prevented in the patient with SLE.

B. Nephrotic and pseudo nephrotic syndrome in lupus nephritis

These patients were kept in bed for varying lengths of time and in one, diuresis ensued spontaneously (#23). High protein feeding (up to 1.5 kg/kilo/day) and dietary sodium restriction were aimed at in all cases, but in almost all of these patients there was fairly severe renal damage, and permanent azotemia necessitated a limitation of the protein intake. The patients with pseudo nephrotic syndrome (#28-30-32) were all extremely ill and required very strict bed rest and meticulous nursing care. One of them (#28) received 500 mg hydrocortisone each day intravenously; the second (#30) was treated

with 75 to 100 mg cortisone daily, and the third (#32) received no steroid. In no case was there any detectable effect of treatment on the outcome.

C Chronic renal failure in lupus nephritis

In general the aim of treatment was to allow the patient to lead as normal a life as possible. In all cases the dietary protein intake was limited usually to about 40 gm daily. The patients were carefully instructed about the importance of an adequate fluid intake and urinary output. The fluid intake (2000-3000 ml/24 hours) was spread through the 24 hours and we insisted that they drank 2 to 3 glasses of water at night before retiring. These two measures in combination were perhaps the most important factors in preventing rapidly advancing azotemia in those with chronic renal failure.

In patients who were treated with corticotrophin or cortisone the sodium intake was kept below 2 gm (85 meq) daily, but sodium restriction has not proved necessary in patients receiving prednisone. Patients with the nephrotic or pseudonephrotic syndromes and some of those with chronic renal failure were limited to 500 mg (22 meq) of sodium daily. Patients with chronic renal failure were closely observed in the outpatient department. Frequent electrolyte determinations enabled us to anticipate and treat serious electrolyte imbalances in some cases. This was usually done by limiting the electrolyte intake in the diet as the need arose. Phosphorus was on occasion limited to 600-800 mg/day and potassium to 1000 mg (25 meq) or less. Sudden and fatal hyperkalemia (#32) cannot always be prevented by dietary means especially when the patient is severely ill and there is wide periodic use breakdown. Ion exchange resins 50% glucose intravenously with insulin and calcium were used to prevent sudden cardiac arrest due to hyperkalemia. Calcium lactate in doses of 9 gm daily and vitamin D 10,000 units daily were given to patients in whom the levels of serum calcium were low. Supplementary sodium bicarbonate was sometimes necessary to combat hyperchloremic acidosis. Diarrhea and vomiting were well controlled by chlorpromazine. Initially it was given in doses of 25 mg 6 hourly by intramuscular injection. When the vomiting was controlled the intramuscular injections were stopped and the drug was given by mouth.

Anemia may be due to the effects of SLE on the bone marrow or to a hemolytic process (#1). It usually responds well to treatment of the disease with cortisone or corticotrophin (67). On the other hand if anemia was associated with significant azotemia steroids were of no value and transfusions of packed red cells were given. As reactions to blood transfusion are not uncommon in patients with SLE cross matching should be meticulous and Coombs tests should be done routinely. Transfusions should be given only as the general symptoms warrant for no improvement in renal function occurs in the patient whose hemoglobin is raised to normal (251) and Platt has suggested that glomerular plasma flow may be adversely affected by a substantial increase in the hematocrit (227).

Transient hypertension occurred during acute exacerbations of SLE (#2) and usually responded to treatment of the exacerbation with cortisone or corticotrophin. Permanent hypertension occurred infrequently as patients usu-

ally died before the stage of chronic glomerulonephritis. Those with hypertension were treated with small doses of reserpine and/or pentolinum. The history of case #31 (Fig 7) illustrates the successful management of a patient with SLE and chronic renal failure. In October 1953 this 23 year old student was severely ill with grand mal seizures, hypertension, severe acidosis, tetany and anasarca. After recovery from this acute episode he was treated as outlined above and was able to continue working eight hours daily until three weeks before his death in August, 1955. During the whole of this period he was admitted to hospital once at our request and once for blood transfusion.

2 THE EFFECTS OF CORTICOTROPHIN AND CORTISONE ON LUPUS NEPHRITIS

In 1951 Rich and his co-workers reported that the development of experimental anaphylactic nephritis in rabbits (242) was prevented by the administration of corticotrophin (ACTH) (23-241). When cortisone was given instead of ACTH anaphylactic nephritis did not develop, however a different type of lesion appeared (240). Subsequently they showed that these lesions were produced by cortisone alone (241). The lesions were characterized by dilatation of the glomerular capillary loops, focal necrosis of cells of the loops, and the formation of large hyaline masses in the tufts. There was frequent rupture of the tufts and considerable hemorrhage in the tubules. The lesions were similar in appearance to the glomerular lesions in diabetes mellitus described by Kimmelstiel and Wilson (142). Bloodworth and Harway (30) and Wilson and Stumpf (301) have also produced similar lesions in rabbits with cortisone. Harvey and his colleagues (110) stated that they had observed similar lesions in one patient with SLE, but no histologic description was given.

Without doubt corticotrophin and cortisone are of great value and may be life saving in acute exacerbations of SLE (42, 55, 67, 266, 269). The early experiences of numerous investigators (41, 42, 45, 71, 118, 266, 268, 288) led them to conclude that the renal lesions of SLE were seldom benefited by corticotrophin or cortisone. Dubois (67) and Haxerick (113) however noted a decrease in the hematuria and proteinuria in some patients given large doses of cortisone, but in three patients with SLE treated with cortisone Jancovay (125) noted a marked exacerbation of the renal picture as determined from the Addis count. Particularly noticeable was the tremendous increase in albuminuria. When these three patients were treated with ACTH there was very little alteration in the renal picture. Soffer and Bader (216) observed that hematuria and edema persisted despite treatment. In five of their ten patients with azotemia the blood urea nitrogen returned to normal levels when the patients were rehydrated and their clinical condition had improved. Harvey and his colleagues (110) made similar observations and at the post mortem examination of several patients treated with corticotrophin and cortisone for long periods of time they found no renal disease. Recently Bollet, Segal and Bunim (31) treated four patients with SLE and lupus nephritis with up to 30 mg of prednisone daily. They found no improvement in the renal status and no significant change in the quantity of proteinuria.

Dubois (66) reported that the early 'mild nephropathy' cleared with treat-

ment. Two of his patients improved after treatment with cortisone but evidence of renal involvement appeared again during exacerbations a few months later. Soffer and his co-workers (269) did not observe an increased rate of progression of the renal lesions as a result of corticotrophin or cortisone therapy in 50 patients. They also emphasized that hormonal therapy had no effect on the hypertension associated with underlying renal disease. On the other hand Harvey (110) observed elevation of the blood pressure and rapid accumulations of fluid in seven patients with SLE and lupus nephritis who were treated with corticotrophin and cortisone. In five the change was so rapid that hormonal therapy had to be stopped.

In a small number of patients with SLE treated with hormones Soffer (269) observed a significant improvement in renal function. Heller, Jacobson and Hammarsten (118) studied the protein excretion, urinary sediment and tests of discrete renal functions in two patients with SLE and in four patients with glomerulonephritis. They concluded that cortisone had no beneficial effects upon the basic pathologic process in the glomerular capillaries.

Of the present series of 33 patients 22 had received corticotrophin or cortisone before the first biopsy was made (Table V). Seven had histologic evidence of severe kidney damage and in eight the kidneys were normal. Eleven patients had received no hormone therapy before the first biopsy. Five of this group had pathologic evidence of severe kidney damage and in three the kidneys were normal. In twenty one patients serial histologic examinations were made (Table VI). A decrease of kidney damage assessed histologically was not observed in any patient. Seventeen patients were treated with hormones between the time of the first and the last histologic study. The doses used were those which were sufficient to suppress symptoms and in no case did the maintenance dose exceed 200 mg of hydrocortisone daily or its equivalent. Of the sixteen patients the renal lesion progressed and in

four patients were not treated at the last histologic study. It is noted whereas in the other logic material we did not find by cortisone in rabbits.

The numbers of patients treated with cortisone. Unfortunately we did not follow to the kidney following treatment we can find no evidence of the renal lesion for was the same in those patients who had never received

The literature on prognosis elsewhere (110-184)

starting point of the disease. Until recently SLE was considered to be an acute or subacute disease, and the less dramatic symptoms and signs which may have been present for years were overlooked. With increasing interest in and experience of the disease it has now been recognized that past episodes such as Raynaud's phenomenon, arthralgia, thrombocytopenic purpura and hemolytic anemia were not independent disease entities but were due to activity of SLE (290). Moreover, as pointed out by Moore and Lutz (196) and by Haverick and Long (114), biologic false positive serologic tests for syphilis may be observed for many years before the patient develops symptoms or signs of SLE. Thus it is apparent that it may be difficult or impossible to date the onset of SLE which does not necessarily coincide with the appearance of the first florid attack of the disease.

Evidence that SLE is frequently a chronic rather than an acute or subacute disease was presented in 1953 by Merrell and Schulman (184). In their series of 99 patients the time between the estimated onset and the date of diagnosis varied from less than one month to 35 years. Analysis of their data reveals that this latent period was over ten years in twelve patients, it was from five to ten years in seventeen patients, from two to five years in twenty-six patients, and it was two years or less in forty-four patients. Bach, Klempner and Schifrin (9) reported that the maximum survival time was 41 years from the time of onset but this report is twenty years old and more recent reports contain numbers of cases in which the disease has been present for many years (22, 110, 111, 127, 290). As the course of the disease may be so prolonged and as the initial symptoms may be insidious and are extremely variable it is often difficult to define exactly the date of onset. The duration of the disease from the appearance of the first symptoms to the time of our initial study is shown graphically in Figure 34. In most, but not all cases the time of our initial study corresponded closely with the time of diagnosis. From Figure 34 it will be noted that in the majority of cases (57%) the duration was less than two years, but that in four cases (12%) it was between five and ten years, and in five cases (15%) it was between ten and fifteen years. Because of the difficulty in assigning an exact

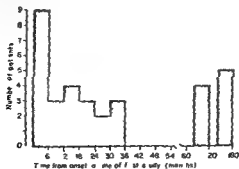


FIG. 34 Histogram showing the length of time from the onset of the first symptom of SLE until the date of the first renal biopsy done in 33 patients with SLE.

date of onset in these patients, it is likely that these figures are somewhat inaccurate. If so they err in underestimating the duration of the disease.

Harvey and his colleagues (110-196) studied two specific factors with respect to their effect on prognosis—namely, age at the time of diagnosis and the duration of time from onset to diagnosis. They found no significant difference between the survivorship curves of patients under and over 40 years of age and in respect of the second point, they concluded that 'the type of case that presents serious enough symptoms early in its course to bring the patient to the attention of the doctor and enable him to make a diagnosis may well be the type that progresses more rapidly thereafter.' Our series is too small to analyze in respect of these two general points of age and duration of the disease but much can be gleaned from a close study of the course of a single manifestation of the disease—namely, the renal involvement.

2. PROGNOSIS IN LUPUS NEPHRITIS

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ever protein and formed elements may appear in the urine of patients with SLE during acute exacerbations (110-269) and these abnormalities may disappear either when spontaneous remission occurs (273) or as a result of therapy (42-110-269). This has been our experience.

Keith (140) in 1940 did not believe that renal insufficiency played an important role in causing death but the opposite view had been advanced by Snapper in 1935 (265). He drew attention to the importance of the renal lesion

depicted below.

In Table XVII findings on 33 patients are presented. The patients will be discussed on the basis of the clinical and pathologic criteria previously described. When first studied eleven had normal kidneys. Nine are still living, one (#8) died of an acute exacerbation of SLE and the other (#11) of acute anterior poliomyelitis. She was not azotemic at the time of her death but a membranous lupus glomerulonephritis was found at post-mortem examination. None of the ten patients with mild lupus nephritis (glomerulitis) has died but four (#14-18-19-21) have developed clinical and pathologic evidence of progressive renal involvement.

Twelve patients had severe lupus nephritis (glomerulonephritis) when first studied. Eight have since died and only one (#29) enjoys moderate health despite a mild degree of azotemia. Six of these patients had the nephrotic syndrome and four have died in uremia. Of the others two (#24-29) have mild azotemia and impairment of renal function. Three patients had the pseudo-nephrotic syndrome (proteinuria, hypoalbuminemia, edema and low serum cholesterol). All died within weeks of the onset of edema. The gravity of the

TABLE VIII

Duration of illness and clinical study of 53 patients with SLE a clinicopathologic presentation

Mode of Presentation	Number of Patients	Duration of Illness Before Entry Study*	Duration of Study*	Number Living				Number Dead
				Mode rate health	Ill health	Prognal ovov	Total	
I Normal kidneys	11	45 (3-180)	11 7 (3-23)	6	3	0	9	2
II Glomerulitis	10	26 (3-132)	12 2 (3-23)	5	5	4	10	0
III Glomerulonephritis	12	46 (3-180)	6 5 (1-24)	1	3	4	4	8
(IIIa) Nephrotic syndrome	7	30 (3-72)	12 0 (1-24)	1	2	2	3	4
(IIIb) Pseudo nephrotic syndrome	3	6 (5-6)	0 5	0	0	0	0	3

* Average in months for the group. Range given in parentheses.

prognosis in SLE with the nephrotic and pseudo nephrotic syndrome is thus clearly shown, and these results confirm the findings of Daugherty and Biggenstos (63) and of Sicarn and Profsky (209).

In essence thirty-three patients with SLE have been followed for periods of up to two years. Ten have died within this period giving an overall mortality rate of 30%. Of those who died six died of severe renal failure and one of acute pancreatitis due to fibrinoid necrosis of pancreatic vessels. This patient (#27) who had the nephrotic syndrome was severely uremic. Another died of an acute attack of SLE and myocarditis (#28). She had pseudo nephrotic syndrome, azotemia and severely damaged kidneys. Patient #11 had developed renal damage but was not in renal failure when she died from intercurrent acute anterior poliomyelitis. Patient #8 died from an inadequately treated exacerbation of SLE (acute lupus erythematosus). She was the only patient in whom there was no evidence of lupus nephritis.

V THE RELATIONSHIP OF SLE AND GLOMERULONEPHRITIS TO OTHER DISEASES

1 GLOMERULONEPHRITIS

Few modern texts of medicine mention SLE as a possible cause of renal disease simulating glomerulonephritis, acute, subacute or chronic. As SLE has become a more common—or more commonly recognized—clinical entity its relationship to glomerulonephritis has assumed an increased importance. In recent years many authors have pointed out that the presence of a skin rash is not a *sine qua non* for the diagnosis of SLE and skin rashes are not infrequently absent in patients with lupus nephritis. This was first reported by Brenner (35) and subsequently stressed by Hamburger (107). Recently Marmont (178) reported five cases of SLE without a skin rash, two had proteinuria and the other three died in renal failure.

If no skin rash is present, other symptoms and signs may be overlooked, if they are found their full importance may not be realized. Milne (187) rightly stressed the necessity of a broad clinical perspective in arriving at the correct diagnosis. The following case history illustrates this point.

Case #32

RD (R & E 42597) an attractive 18 year old high school student had enjoyed good health until June 1954. After a period of exposure to the sun she developed erythematous spots on the forearms and face. In July she had transient ankle edema which recurred one month later. Gross proteinuria and hematuria appeared a diagnosis of Bright's disease was made and she was confined to bed. On November 1st she was admitted to the University of Illinois Hospital where periorbital and pretibial edema was noted. Much blood and protein was found in the urine a few leucocytes and many hyaline granular fatty and erythrocyte casts were seen in the urinary sediment. The serum albumin was 2.3 gm/100 ml the serum globulin was 3.3 gm/100 ml the blood cholesterol was 132 mg/100 ml and the BUN was 98 mg/100 ml. She was able to concentrate her urine to a specific gravity of only 1.015 the urea clearance was 11% of ANRF, and the excretion of P₂₅P was 3% in 15 minutes. A diagnosis of subacute glomerulonephritis was made.

However careful review of the history revealed the following additional information. At the beginning of the illness she was feverish and had noted arthritis of the interphalangeal joints. In October she had pain in the shoulder joints and complained of pleuritic pain. On examination there was a persistent fever, a faint butterfly face rash was detected the liver was enlarged, there were effusions into pericardial, pleural and peritoneal cavities the leucocyte count was 3500/mm³ and the thymol turbidity was 12 units. This additional evidence made a diagnosis of SLE with lupus nephritis very probable and many Hargraves cells were found on examination of the bone marrow. She became comatose had several convulsions and died on November 15. Permission for a full postmortem examination was refused but kidney tissue was obtained postmortem with a biopsy needle.

Postmortem Biopsy (Color Plate—Fig 9) The glomeruli were ischemic and there were local areas of irregular smudgy thickening of their basement membranes. Local areas of hypercellularity were also seen. The lumina of a few glomerular capillaries were filled by homogeneous eosinophilic material these capillary thrombi were PAS positive and stained red in Mallory preparations (Color Plate—Fig 10). Distinct wire loops, karyorrhexis and hematoxylin bodies were seen in a few glomeruli (Color Plate—Fig 9). A few adhesions between glomerular tufts and Bowman's capsule were noted. Proteinaceous material was observed in Bowman's spaces and in the convoluted tubules whose lining epithelium showed considerable atrophy and degenerative changes. There was edema and fibrosis of the interstitial tissue which was infiltrated by chronic inflammatory cells. There were fibrotic changes in the small arteries.

Diagnosis: Lupus nephritis subacute local and generalized membranous and proliferative glomerulonephritis

The pathologic differentiation of lupus nephritis from glomerulonephritis may be difficult (Section VI (2E) and Table XI). In the early stages of the condition the local involvement of small areas of the periphery of the glomerulus by membranous and proliferative changes (Color Plate—Fig 1) has been, in our experience, peculiar to lupus nephritis, whereas in glomerulonephritis the whole or almost all of the glomerulus is usually involved. Nonetheless we have seen lesions in the early stages of glomerulonephritis, which have been difficult to distinguish from those of lupus nephritis. For example, in Enticknap and Joiner's excellent clinical and pathologic study of Bright's disease (75) Figure 1 is taken

from the kidney of a patient diagnosed clinically as Ellis type I nephritis. A pathologic diagnosis of Ellis type II nephritis was made by the electron microscope. Local areas of necrosis, local hypercellularity and karyorrhexis in the glomeruli and thickening of the glomerular basement membrane are prominent features. Unfortunately the clinical history of this patient was not given but the pathologic features are more consistent with the diagnosis of lupus nephritis.

In his Croonian lectures in 1942 Arthur Ellis wrote: "Much of the knowledge which still exists in our knowledge of the conditions grouped under the term Bright's disease arose from failure to study the natural history of the disease in its various conditions—their mode of incidence and subsequent course to death." (1) Case 31 (page 42) is an excellent illustration of the value of the study of the natural history of renal disease and the importance of persistence in arriving at an exact pathologic diagnosis. In September 1901 the patient developed symptoms and when seen by us for the first time she had the classical clinical and laboratory picture of SLE. From the examination of her urine a renal biopsy made in September 1903 was consistent with the diagnosis of lupus nephritis (Color Plate—Fig 7). Fibrinoid deposits were seen in the glomerular basement membrane and in the arterioles in certain areas of karyorrhexis. A second biopsy in April 1904 revealed a picture consistent with chronic lupus glomerulonephritis respectively. From this time on the clinical and laboratory course came more and more to resemble that of a case of chronic glomerulonephritis without SLE and in October 1905 the renal lesion was quite indistinguishable from that of chronic glomerulonephritis.

Had the diagnosis of lupus nephritis been made at the time of the first biopsy, the course of the disease would undoubtedly have been made. Yet taking into account the clinical and laboratory and pathologic features studied serially over a period of five years there was no doubt that this was a case of SLE with lupus nephritis.

2 POLYARTERITIS NODOSA

Polyarteritis nodosa may run a prolonged remittent course and like SLE affect many organs and systems of the body. Consequently the differential diagnosis may be a difficult one as has been emphasized by Banks (14), Kump (15), Mier (131), Pagel (219) and others. In 1928 Volk (293) reported a case of clinical SLE in whom lesions characteristic of polyarteritis nodosa were found post mortem. Recently Lincoln and Ricker (169) and Kofman, Johnson and Zinnerman (156) reported cases of histologically proven polyarteritis nodosa in whom Hargraves's cells were found.

We have observed three patients in whom the problem of the relationship between polyarteritis nodosa and SLE arose. Case #10 had features common to both diseases. Hargraves's cells were found on examination of the peripheral blood and polyarteritis nodosa was found on examination of a muscle biopsy. The following case is presented because her clinical course was typical of that

nodosa runs a prolonged course characterized by exacerbations and remissions. It is a recurrent progressive inflammatory disease of the muscular type of arteries. Fibrinoid necrosis was a prominent pathologic feature and involvement of the kidney almost universal (29, 154, 307). Renal infarcts were the prominent pathologic lesion but were not extensive enough to result in renal insufficiency. A similar pathologic picture was described by Dawson, Ball and Platt in five of their cases (their Group B) (64).

The lesions described in hypersensitivity angitis by the Cincinnati workers were very different (154). A necrotizing glomerulonephritis was found in nine of their ten cases. Exudation and necrosis rather than proliferation of epithelium and endothelium characterized the glomerular lesions and as the process was acute no evidence of healing was seen in any of the lesions. Dawson, Ball and Platt described a similar but not identical lesion in eight cases (their Group A) (64). There was patchy fibrinoid necrosis of the glomerular tufts but with varying amounts of epithelial crescent formation and partial fibrosis of the tufts. Four similar cases were later added by Wainwright and Dawson (297). Urinalysis is not helpful in differentiating the two diseases. As has been shown by Schreiner (255) and Hamburger (107) even the telescoped urinary sediment may be found in both conditions and in other forms of glomerulonephritis. In these circumstances can renal biopsy be of assistance in the differential diagnosis of SLE and polyarteritis nodosa?

The lesions described by Zeek as polyarteritis nodosa are obviously very different from those of SLE and their focal distribution and nature makes it unlikely that a positive diagnosis could be made in all cases by renal biopsy. The necrotizing glomerulonephritis described by both the Cincinnati and the Manchester workers however is very similar to the glomerulonephritis seen in some cases of SLE and in one of her cases Zeek found some features of SLE (154). Patients with the necrotizing glomerulonephritis of hypersensitivity angitis are acutely ill and the course is a rapid one. In those patients with SLE and lupus nephritis who were acutely ill and in whom the clinical course was

difficulties involved in making an accurate histologic diagnosis are illustrated well in case 5 reported by Pagel and Treip (219). In this patient, a 46 year old man, the clinical diagnosis was either polyarteritis nodosa or SLE. The patient died of rapidly progressive renal failure—a finding more in keeping with the diagnosis of hypersensitivity angitis. On the basis of the distinctive wire loop phenomenon, Pagel and Treip concluded that the pathologic diagnosis was SLE. No hematoxylin bodies were found. We have shown that the wire loop lesion occurs in a variety of diseases and in patients with lupus nephritis running so fulminating a course hematoxylin bodies have been found in the areas of local necrosis (28, 30, 32) as Smith (264) has also pointed out. We conclude therefore that the diagnosis in Pagel's case was probably not SLE but Zeek's hypersensitivity angitis.



FIG 37 *Kidney from a patient ill with long standing rheumatoid arthritis (R&F Autopsy 69/1915)* Note the diffuse hypercellularity of the glomerular tufts due to endothelial cell proliferation (H&E $\times 230$) This type of diffuse glomerulitis resembles that observed in some instances of lupus nephritis (compare Fig 23)

3 RHEUMATOID ARTHRITIS

Joint pains and arthritis are prominent features of the symptomatology of SLE. Mild arthritis is common but more severe degrees with marked deformities of the joints are unusual. The kidneys are frequently affected in SLE but clinical involvement of the kidneys in rheumatoid arthritis is not significant. Although few pathologic studies have been made in rheumatoid arthritis Cobb, Anderson and Bauer (54) observed that renal disease was notably frequent. Pirani and Bennett (225) found a proliferative glomerulitis in two of three cases (Fig 37) and Baggenstoss and Roenbergs (13) were impressed by a high incidence in autopsy material of a specific diffuse proliferative glomerulitis. They speculated that the agent responsible for rheumatoid arthritis might also be responsible for a low grade subclinical glomerulitis (13). That this may be a terminal phenomenon is suggested by our own biopsy studies in twenty-two patients with rheumatoid arthritis in none of whom were the glomeruli abnormal (230).

Rheumatoid arthritis is a generalized disease and on occasion needs to be differentiated from SLE. Laboratory tests may afford little help in both diseases the globulins may be elevated the thymol turbidity and other flocculation tests may be positive (156, 163, 230) and Hargraves cells may be found on examination of the bone marrow or peripheral blood (82, 120, 182, 208, 263). At the present time the exact relationship between the two diseases is a matter for speculation. Humans and his colleagues (120) found Hargraves cells in 54

of 455 cases (12%) of rheumatoid arthritis, and have suggested that some cases of rheumatoid arthritis may in fact be suffering from SLE.

The following patient had rheumatoid arthritis for ten years before developing SLE and lupus nephritis:

Case 23

J.M. (R & E 427706), a 47 year old laborer, had had intermittent attacks of conjunctivitis for 26 years. In 1914 he first developed arthritis which involved symmetrically the interphalangeal, wrist, elbow and ankle joints. He was treated for rheumatoid arthritis. Apart from recurrent attacks of arthritis resulting in some deformity, he had no symptoms until the fall of 1954 when he complained of pleuritic pain and increasing shortness of breath. In January, 1955, he developed a fever and was admitted to hospital acutely ill and anemic. There was much edema of abdomen, sacral region and legs and he had ascites and bilateral pleural effusions. The pulse was rapid, the blood pressure was 155/95 mm Hg, the heart was enlarged, a Grade III blowing systolic murmur was heard at the apex and there was electrocardiographic evidence of myocarditis. Liver, spleen and lymph nodes were enlarged and on examination of the bone marrow many Hargraves cells were found. His condition improved rapidly after treatment with digitals, low salt diet, and cortisone, but protein and hyaline casts were persistently found in the urine. The maximum urinary specific gravity was 1.018, and the NPN was slightly elevated. After leaving hospital on February 11 he was much improved, but still had intermittent chest pain and pains in the joints.

In June 1955, he had a front face rash, was anemic and the white cell count was low. The

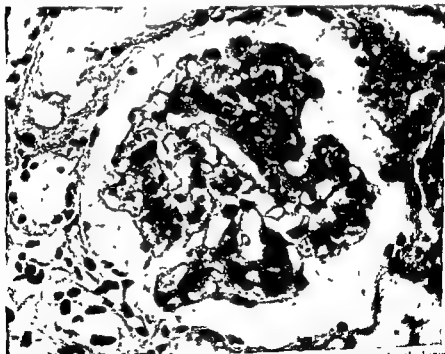


FIG. 22. Patient #22, First Biopsy, February 1955. Note the smudgy, irregular thickening of the glomerular basement membrane. This is strongly suggestive of fibrinoid. In some areas there is obliteration of the capillaries, hypercellularity and slight karyorrhexis (early local necrotic lesion). (H&E $\times 500$)

heart was slightly enlarged. Liver, spleen and lymph nodes were not palpable. There was protein ++ in the urine, and many erythrocytes, leucocytes and cellular, hyaline and fatty casts in the urinary sediment. Tests of renal function were normal. From July to November 1955 he had recurrent attacks of arthritis and purpura, was feverish, and had several small hemoptyses. When admitted to hospital in November he was acutely ill, feverish and complained of pain in the chest and in the joints. There were many purpuric blotches on the skin of the arms and legs; his legs were edematous; the liver was enlarged; the heart was enlarged and the blood pressure was 150/100 mm Hg. The urine contained +++ protein and the microscopic urinalysis was unchanged. His symptoms improved after the dose of prednisone was increased to 25 mg per day.

Renal biopsies were made on February 23, June 16 and November 14, 1955.

The first renal biopsy (February 1955) (Fig. 38) contained ten glomeruli; their surrounding tubules and some medulla. Most glomeruli were slightly ischemic and lobulated and there was a local irregular thickening of their basement membrane. This was smudgy in character suggesting fibrinoid. "Wire loop" lesions were noted in a few places. Mild local hypercellularity and occasional karyorrhexis were observed in a few glomeruli. In these areas the capillary lumina were obliterated and a few adhesions between the tuft and Bowman's capsule were noted. No hematoxylin bodies were seen. The convoluted tubules were slightly dilated in places and there were distinct degenerative changes of their lining epithelium. Proteinaceous material was present in Bowman's spaces and in the tubular lumina. There was slight interstitial edema and fibrosis and a small number of chronic inflammatory cells infiltrated the interstitial tissue.

Diagnosis: Local and generalized membranous glomerulonephritis.

Second Renal Biopsy (June 1955) (Fig. 39) Five glomeruli with their surrounding



FIG. 39 Patient #22. Second Biopsy, June 1955. In both glomeruli note the irregular smudgy thickening of the basement membrane. It is local in the glomerulus on the left, diffuse in that on the right. A well organized adhesion can be seen between the glomerular tuft and Bowman's capsule in the glomerulus on the right, this is probably the end result of local necrosis in this area. There is a moderate degree of interstitial edema and tubular degeneration. (H&E \times 350)

tubules were included in the sections. The glomeruli were ischemic and somewhat lobulated. There was a rather marked local thickening of the basement membrane which was smudgy and granular in places suggesting fibrinoid. In places this thickening was quite marked with obliteration of the capillary lumina. There were adhesions between the glomerular tufts and Bowman's capsule. There was minimal local hypercellularity, and occasional karyorrhexis in these areas. Abundant proteinaceous material was found in Bowman's spaces and in the lumina of the convoluted tubules which were dilated in some places and atrophic in others. The tubules were lined by a low cuboidal epithelium in which distinct degenerative changes were seen. A few tubules were completely filled by pale bluish homogeneous casts which stained strongly positive with the PAS technique. There was edema and fibrosis of the interstitial tissue which was infiltrated by a small number of chronic inflammatory cells. The changes were more severe than in the first biopsy.

Diagnosis: Local and generalized membranous glomerulonephritis

Third Renal Biopsy (November 1955) (Fig 40) Twelve glomeruli, their surrounding convoluted tubules and a little medulla were included in the sections. There was irregular local thickening of the basement membrane of all glomeruli. It was smudgy and granular in appearance resembling fibrinoid, occasional 'wire loops' were seen. In some glomeruli the capillary loops had collapsed in areas and were necrotic, fibrinoid material nuclear

There were moderate degenerative changes in the tubular epithelium. There was much

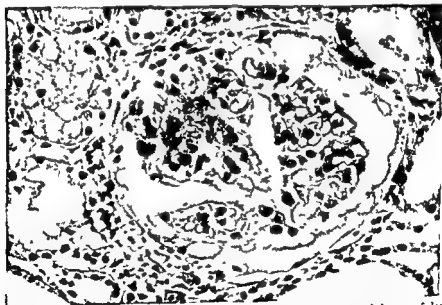


FIG 40 Patient #22, Third Biopsy November 1955. Note a typical lesion of local necrosis with adhesions to Bowman's capsule. Within this area note the smudgy fibrinoid material. "Hematoxylin" bodies are present but cannot be clearly seen in this black and white photomicrograph. In the remainder of the glomerulus slight thickening of the basement membrane is evident. Bowman's space contains proteinaceous material. Note the vascular degeneration of an adjacent convoluted tubule (H&E $\times 500$).

partly fibrous of the interstitial tissue which was infiltrated with a moderate number of chronic inflammatory cells. There was mild thickening and sclerosis of the walls of the small arteries and arterioles; in some there were changes suggestive of fibrinoid. These findings were confirmed in Mallory and PAS preparations. The lesions were more marked than in the second biopsy.

Duquesnoy Local and generalized membranous glomerulonephritis diagnostic of lupus nephritis

4 SCLERODERMA AND DERMATOMYOSITIS

According to Klemperer the morphologic evidence permits the conclusion that generalized scleroderma (progressive diffuse sclerosis) is characterized anatomically by a fundamental implication of collagenous tissues (144). The sclerotic process can be traced to the connective tissue framework of the organs and appears to be the result of an increase in collagen fiber formation; despite widespread hyperplasia of the connective tissue fibers there is no concomitant fibroblastic activity in any phase of the morbid process (148). Nevertheless fibrinoid alterations have been observed in association with the progressive sclerotic transformation of the collagenous tissues, and as Moore and Sheehan (195) have shown both changes are commonly found together in the kidney. Klemperer himself points out that the sclerosing change observed in scleroderma is not specific to that disease and is a common finding in the spleen, pericardium and retroperitoneal tissues of patients with SLE (152). Thus it is not surprising on morphologic grounds to find that in some patients there may be no clear cut differences between SLE and scleroderma, and that rigid classification may be impossible. Recently Richards (243) reported a patient in whom the clinical features were those of SLE but who had scleroderma of the fingers, and Tumulty (290) also mentioned skin changes resembling those of scleroderma in patients ill with SLE. This problem also arose in the case reported by Volpe and Hauch (294). Their patient diagnosed by them as suffering from scleroderma was diagnosed elsewhere as SLE when many Hargraves cells were repeatedly found on examination of the bone marrow. From the clinical history it is perhaps more likely that the patient was suffering from SLE. Surely we can admit that she presented features of both illnesses. We encountered a similar problem in one of our patients.

Case

In 1957 (11-17-57) a light-skinned, 39-year-old negro female had a 2-year history of migratory joint pains affecting the interphalangeal, knuckle and knee joints. Two years later she suffered from myalgia and myositis and complained of shortness of breath. All lymph nodes were enlarged and on entry of a lymph node biopsy hyperplastic lymphoid reaction was found.

In July 1953 a butterfly face rash appeared after exposure to the sun. She ran a low grade fever and edema of the face and pretibial regions was noted. The lymph nodes and liver were now enlarged. The patient was anemic and had a pericardial effusion, and the serum globulin level and LSR were raised. Hargraves cells were not found on examination of the bone marrow, but a biopsy from the skin of the face was considered to be compatible with lupus erythematosus. When she was treated with cortisone her symptoms improved considerably.

Following this however she continued to have intermittent joint pains and recurrent pleural pain was troublesome. She lost much hair from the scalp.

When seen again in July 1951 there was atrophy of the skin in patches in the butterfly area of the face. The lymph nodes were enlarged and a pericardial effusion was found. The thymol turbidity was 12 units and Hargraves cells were found in the peripheral blood. At this time however a new and striking feature had appeared. The skin of the forearms and of the fingers was tense shiny atrophic and indurated and multiple paronychia were prominent. A skin biopsy revealed dermal fibrosis.

By August 1955 she had become very weak and fatigued easily and she had developed severe Raynaud's phenomenon. The skin had become thick and indurated. Areas over the hands were white and tender and the skin was firmly bound down. The liver was enlarged and tender and tests of liver function were abnormal. Hargraves cells were repeatedly found in the peripheral blood. On barium swallow severe esophageal changes typical of scleroderma were seen. A skin biopsy showed changes characteristic of scleroderma. Renal biopsies made in October 1953, September 1954 and August 1955 were reported as essentially normal.

The initial diagnosis in this patient was SLE. This was made because of the intermittent febrile course, the development of a typical face rash, the affection of lymph nodes and liver, and of the joints, pleura and pericardium. The serum globulin and thymol turbidity were raised, the skin biopsy was consistent with the diagnosis and Hargraves cells were repeatedly found. And yet at a later stage findings typical of scleroderma were noted. We are driven to conclude that this patient suffers from a diffuse collagen disorder with features of both SLE and scleroderma.

The pathology of the kidneys in generalized scleroderma was described by Masugi and Ya Shu in 1938 who were the first to point out that extensive fibrinoid changes could occur in the connective tissues of the arterioles and glomeruli (179). Two years later, Pollack described two cases of scleroderma with extensive fibrinoid changes in the vessels (228) both had severe renal involvement and in one the lesions resembled those seen in SLE. In his discussion of Pollack's paper Bachr stated that both patients had a long intermittent febrile course, persistent hematuria, involvement of the synovial membranes of the joints and involvement of pleura, pericardium and peritoneum. Leucopenia and depression of the hemoglobin were found in one. On the other hand as a result of their experience of 150 cases of scleroderma Leinwand *et al* (165) have pointed out that hematuria does not occur for long periods and usually develops only in the terminal stage of the illness, whereas one of our patients (#23) with SLE had prolonged hematuria for about one year. Thus despite the typical skin lesion the clinical course of the patients described by Pollack more closely resembled that of SLE than that of scleroderma and it is probable that they had features of both diseases.

The clinical evidence favors scleroderma.

The pathology of the renal lesion has been described by Masugi and Ya Shu (179), Bevans (27), Goetz (94), Moore and Sheehan (196), Leinwand

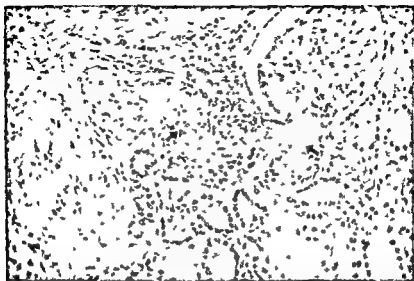


FIG 41 Kidney from a patient with scleroderma who died with severe and rapidly progressive renal failure (R&E Autopsy 130 1956) Note the marked intimal thickening in the small artery on the left and almost complete obliteration of the lumen The mucinous-like character of this thickening is not clearly demonstrated in this black and white photomicrograph Distinct fibrinoid changes are seen in the thickened wall of the arteriole (arrows center and right) extending into the glomerulus Note also the diffuse thickening of the basement membrane in the glomerulus (H&E $\times 150$)

(165), and recently by Rodnan and his colleagues (244) The lesion affects the origins of the intralobular arteries, where a concentric mucinous like thickening of the intima may be so severe as to stretch the media of the vessel (Fig 41) When severe these lesions result in a widespread focal cortical infarction which gives the lesion its patchy character Fibrinoid necrosis is often seen at the peripheral portion of the intralobular arteries and may extend distally from there into the glomerular tufts (Fig 41) As not all arteries are affected the lesion is patchy in its distribution and areas of normal kidney are found between areas which are grossly damaged Moore and Sheehan rightly observe that this lesion differs from that seen in the other so called collagen diseases

Dermatomyositis has been considered by some authors to be akin to scleroderma but others have regarded the two diseases as distinct clinical entities (65) In 1940 Keil described in detail five cases which he considered showed transitional features between dermatomyositis and SLE (138) These patients all had long and complicated clinical histories but despite the completeness of the protocols it is impossible to be certain that any of them was suffering from SLE Postmortem examinations in two of them did not reveal any lesions diagnostic of SLE

Renal disease has rarely been reported in dermatomyositis Talbot and his colleagues reported a single case in 1939 (282) Originally the diagnosis was

scleroderma and a skin biopsy had shown features "similar to those observed in some cases of muscular weakness associated with arthritis and scleroderma." In the last week before this patient's demise there occurred a sudden deterioration in renal function—which had previously been normal. The postmortem diagnosis was "chronic diffuse dermatomyositis with scleroderma." The authors commented on the renal lesion as being in their experience, unique. There was a widespread focal cortical infarction, but the glomeruli within these degenerating areas were preserved. The medullary and arcuate branches of the renal artery were normal, but the intralobular arteries showed an infiltration of their subintimal substance by a mucinous material, these lesions ceased abruptly when the vessels assumed the caliber of afferent arterioles. Fibrinoid necrosis was seen in a few arteries. This renal lesion resembles very closely that described later in scleroderma, both clinically and pathologically (163, 190, 244), and cannot be considered to be due to dermatomyositis *per se*. Keil reviewed the published cases of dermatomyositis (139) and concluded that the kidneys are, as a rule, spared in dermatomyositis," although he himself had referred to the rare occurrence of gross hematuria, azotemia, and hypertension. Recently Domzalski and Morgan were unable to adduce any further evidence of kidney involvement in dermatomyositis (65).

5 THROMBOTIC THROMBOCYTOPENIC PURPURA

outcome within at most eight weeks (262). The clinical picture is usually episodic and is characterized by thrombocytopenic purpura, severe hemolytic anemia, and bizarre and transitory neurologic signs. These clinical findings may also occur as manifestations of SLE.

Thrombotic thrombocytopenic purpura is sometimes associated with other so-called collagen diseases (262), and a number of cases have been reported in which there were features of thrombotic thrombocytopenic purpura and of SLE (17, 18, 46, 161, 279, 280, 299). The following case was diagnosed clinically as suffering from SLE. At the postmortem examination lesions of both SLE and thrombotic thrombocytopenic purpura were found.

RS (R & E 40,315) a 31-year-old television repair man had had diabetes mellitus since 1930. Nevertheless his health was good until 1952 when swelling of the joints of his fingers occurred. Thenceforward he had intermittent attacks of pain and swelling involving the fingers, wrists, elbows, knees, and ankles. In May 1953 he had a thrombolytic of the right leg. One year later a diagnosis of rheumatoid arthritis was made when pain and swelling of the joints recurred. Because he had attacks of severe pleuritic pain and the Wassermann reaction was positive the diagnosis of SLE was considered but Hargraves cells were not found.

Subsequently he had episodes of fever and lethargy. In October 1955 he had chills, was feverish, and complained of severe generalized abdominal pain which persisted until his admission to hospital on November 14, 1955. He was acutely ill, his temperature was 104° and the pulse rate was 120 per minute with multiple extrastolic. There was a general re-

lymphadenopathy and bilateral pleural effusions petechiae were found in the mouth and on the skin of the chest and abdomen There was generalized abdominal tenderness and marked rebound tenderness but bowel sounds were present The urine specific gravity was 1.031, the urine contained protein ++ no bile and a trace of urobilinogen In the urinary sediment there were many erythrocytes 20-30 leucocytes some of which were in clumps many hyaline and granular and a few leucocyte casts The hematocrit was 30% the leucocyte count was 2200/mm³, and adequate numbers of platelets were seen on a blood smear The serum bilirubin was 0.29 mg/100 ml, serum albumin 3.1 gm/100 ml, serum globulin 2.0 gm/100 ml (gamma globulin 1.05 gm/100 ml) He was diagnosed as having an acute exacerbation of SLE with acute abdominal complications of lupus (229) and was therefore treated with intravenous hydrocortisone 500 mg daily later as his condition improved he was given hydrocortisone by mouth Blood cultures and the Wassermann reaction were negative The leucocyte count was persistently low Later he developed a pericardial friction rub and a systolic murmur was heard at the base of the heart In March 1956 he complained of severe headaches subsequently became comatose had several clonic convulsions and died He did not have purpura at this time

At the postmortem examination a verrucal nonbacterial endocarditis of the mitral valve was found There was moderate hypertrophy of the left ventricle bilateral silicotic pleuritis and acute bronchopneumonitis There were multiple widespread platelet thrombi in the arterioles of myocardium lung brain spleen liver and kidneys There was generalized lymph node hyperplasia and moderate splenomegaly Well marked perivascular fibrosis was seen in the spleen (Fig 42) In the kidneys (Fig 43) the basement membrane of most glomeruli was irregularly thickened the thickening was severe in areas resulting in marked narrowing of the capillary lumina In places the thickened basement membrane appeared smudgy and granular suggesting the presence of fibrinoid Wire loop lesions were seen in some glomeruli There was no cellular proliferation in the glomeruli The convoluted tubules were atrophic in areas and degenerative changes were seen in the lining epithelium

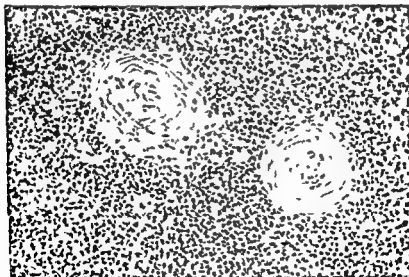


FIG 42 Patient, RS Autopsy Spleen from a patient who had SLE and thrombotic thrombocytopenic purpura Note the luminal perivascular fibrosis in the penicillar arteries This is typical of SLE Note that a small subendothelial platelet thrombus can be seen in the artery on the left (H&E \times 170)



FIG. 43 Patient R.S. Autopsy kidney from a patient who died of SLE and thrombotic thrombocytopenic purpura. Note the severe and diffuse somewhat smudgy thickening of the glomerular basement membrane and the wire loop lesions. To the right of the glomerulus a small artery is completely occluded by a fairly homogeneous platelet thrombus (H&E \times 230).

There was considerable fibrosis of the interstitial tissue in places and infiltration with chronic inflammatory cells. A moderate degree of thickening and hyalinization of the walls of the small arteries and arterioles was noted. The lumina of many were almost completely occluded by irregular smudgy eosinophilic thrombi—some of which were undergoing organization.

Diagnosis: Diffuse and generalized membranous glomerulonephritis consistent with lupus nephritis. Multiple arteriolar platelet thrombi.

A clinical diagnosis of SLE was made because the patient had a prolonged episodic illness with fever, malaise, arthritis, and evidence of involvement of pleura, pericardium and peritoneum. The leucocyte count was persistently low, the Wassermann reaction was positive transiently, and the findings in the urinary sediment were consistent with the diagnosis of SLE. At the postmortem examination a pathologic diagnosis of SLE was made because there was periarterial fibrosis of the spleen, verrucous nonbacterial endocarditis, and the renal lesions were compatible with lupus nephritis. Save for the terminal episode of coma and convulsions there was no clinical evidence to suggest thrombotic thrombocytopenic purpura, yet arteriolar platelet thrombi were found postmortem widespread throughout the organs. A similar case with Hargraves's cells in the peripheral blood and clinical and pathologic features of SLE and thrombotic thrombocytopenic purpura was reported recently by Laszlo, Alvarez and Friedman (161).

Six years ago the opinion was expressed that the lesions of thrombotic thrombocytopenic purpura were "entirely different from those of periarteritis nodosa, disseminated lupus erythematosus and of the usual infectious diseases" (43). Orbison considered it to be a variant of one of the previously characterized collagen diseases stating that "This stand is supported by the prominent aneurysms, large occlusive masses in the arteries and capillaries and the focal destructive lesions of the arteries which characterize this disease are not found in other members of the group [of collagen diseases]" (212). Nonetheless features of SLE or of polyarteritis nodosa have been found in ten percent of the reported cases of thrombotic thrombocytopenic purpura (262) and in one instance features of all three were noted (280). The exact nature of thrombotic thrombocytopenic purpura and its relationship to the other collagen diseases needs clarification.

Capillary and arteriolar damage may be widespread in both SLE and thrombotic thrombocytopenic purpura. Several observers have presented evidence that the vascular damage actually precedes the formation of platelet thrombi in thrombotic thrombocytopenic purpura (6, 99, 212). In our opinion it would seem possible that widespread platelet thrombosis with or without thrombocytopenia and purpura might occur as a complication of the vascular damage in SLE. It is surprising that it is not seen more frequently.

The kidneys are affected often in thrombotic thrombocytopenic purpura. The urine usually contains small amounts of protein, gross or microscopic hematuria and granular casts are frequently found. renal insufficiency and moderate azotemia are quite common (262). Thus examination of the urinary sediment is not helpful in differentiating this condition from lupus nephritis. The differential histologic diagnosis usually presents little difficulty. Eosinophilic thrombi apparently consisting only of fibrin and platelets are found in the arterioles and locally within the glomerular capillaries. In the typical case of thrombotic thrombocytopenic purpura glomerular changes are limited to the areas immediately adjacent to the capillary thrombi and the remainder of the involved glomeruli is normal (10, 262). In contrast with lupus nephritis the only glomeruli affected are those in which the capillaries or arterioles contain platelet thrombi; a large proportion of glomeruli is normal. There are several reports of various forms of nephritis in cases dying of thrombotic thrombocytopenic purpura (60, 99, 204, 299). It is not clear from these reports whether or not the simultaneous occurrence of nephritis and of thrombotic thrombocytopenic purpura in these patients was fortuitous.

II SARCROIDOSIS AND WELCHER'S GRANULOMATOSIS

Before Keil's masterly analysis (136) showing that the simultaneous occurrence of SLE and tuberculosis was fortuitous it was assumed especially in France and in Vienna that the two diseases were related intimately, and that tuberculosis was the cause of death in patients ill with SLE.

The association of cutaneous sarcoidosis and lupus erythematosus has been reported and proven histologically in four patients (93, 189, 275). In recent

years Teilmann has advanced the opinion that there is a definite association between non tuberculous granulomatous lesions and systemic lupus erythematosus. He first described two cases in 1945 (283). In our opinion the findings given in the protocol of the second case are insufficient to warrant a definitive diagnosis of SLE. The first case, a twenty year old girl, had all the clinical features of SLE. At the postmortem examination the kidney lesions were compatible with lupus nephritis, and periarterial fibrosis was noted in the spleen (286). In the lungs multiple nodular subserous giant cell granulomata were found. There was a focal fibrinoid necrotizing process in the interstitial connective tissue and in the walls of vessels, both in the lungs and the lymph nodes. No Schumm bodies were found in the granulomatous lesions. In a later paper Teilmann concluded that the multiphase epithelioid cell granulomata in the serosa together with focal necrotizing and granulomatous processes have to be interpreted as tissue injury specific to the disease [SLE] (284). His pathologic findings have not been confirmed either by ourselves or by numerous other investigators.

Teilmann also considered that the hyperglobulinemia, periarterial fibrosis of the spleen and wire loop lesions of the glomeruli in SLE were expressive of a primary allergic hyperglobulinosis in the reticulo endothelial system analogous to the morphologic humoral reaction in Boeck's sarcoid (286). In our opinion the clinical and pathologic similarities between the two diseases are at best superficial. Despite the relative frequency of SLE and sarcoidosis their simultaneous occurrence in the same patient is so rare that it should be considered fortuitous. Recently we have studied by serial renal biopsies two patients in whom it seemed possible at first that the two diseases might be associated. In the first patient the clinical features of SLE were observed. Hargraves cells were found and the kidney lesions were diagnostic of lupus nephritis. The granulomatous lesions were at first thought to be due to sarcoidosis but were later shown to be due to tuberculosis. The second patient had widespread granulomatous lesions for two years and a diagnosis of sarcoidosis was made by lymph node biopsy. He developed the nephrotic syndrome, and at the first biopsy renal lesions suggestive but not diagnostic of lupus nephritis were found. Subsequently he has been observed for twelve months and no other clinical or biochemical features have suggested the diagnosis of SLE. Thus we can assume that neither patient had both SLE and sarcoidosis. Renal involvement in both diseases is due

from that of lupus nephritis.

In Wegener's granulomatosis the lungs and upper respiratory passages are involved by necrotizing giant cell granulomas (77, 91, 164). Sooner or later in most patients evidence of renal damage appears and about one half of the reported cases have almost invariably involved by this process of capillary loops and scanty polymorphonuclear cell exudation in the

lesion is similar to the local necrotic lesion seen in lupus nephritis. However, in Wegener's granulomatosis more glomeruli are involved, "hematoxylin" bodies are not seen, and granulomatous lesions are found in the interstitial tissue (91). The lesions in the lungs and in other organs bear no morphologic resemblance to those of SLE.

XI THE NATURAL HISTORY OF LUPUS NEPHRITIS

Lupus nephritis is a progressive fatal glomerulonephritis, which at present, is the main cause of death and the most serious problem in patients ill with SLE. In lupus nephritis the glomerular tuft is damaged, and reacts to deposits of abnormal mucopolysaccharides and other proteinaceous substances, with the appearance of local basement membrane thickening ('fibrinoid change,' 'hematoxylin' bodies and endothelial cell proliferation. At any moment in time the kidneys of two thirds of patients ill with SLE are involved to a greater or lesser degree by these pathologic abnormalities and their consequences. The majority of patients ill with SLE die of renal failure and lupus nephritis is found on post mortem examination in over 75 percent. Its course may be fulminating and the patient may die of renal failure within weeks of the clinical onset of the illness. On the other hand lupus nephritis may develop slowly in a patient who has been ill with SLE for months or years or may present with the gradual onset of a classical nephrotic syndrome—which may be the only overt manifestation of SLE. Usually it progresses slowly but inexorably to death during a period of about one to four years. A small proportion of patients may live longer. In general the rate of progression of lupus nephritis is more rapid than that seen in the common forms of glomerulonephritis related to streptococcal illness.

The earliest lesion of lupus nephritis consists of a local membranous glomerulitis involving small areas at the periphery of the glomerular tuft. Small areas of endothelial cell proliferation are also commonly seen. These early lesions have been found by renal biopsy in the absence of signs, symptoms or laboratory data indicating involvement of the kidney. The urine may be normal or it may contain protein, leucocytes in clumps and leucocyte casts—a finding which often leads to the erroneous diagnosis of pyelonephritis.* At this stage of the illness tests of renal function are of little value in making a diagnosis. Renal involvement which can only be suspected clinically may be diagnosed by renal biopsy.

The rate of development of the glomerular changes and the progress of the renal disease may depend on the extent and severity of the initial lesions in the kidney. The progression of the lesion in the glomerulus is indicated by the appearance or increase of fibrinoid material in the basement membrane, by an increase in proliferative lesions, by the development of adhesions between the tuft and Bowman's capsule and in some cases by the development of local areas of necrosis and karyorrhexis. These lesions may mimic the embolic glomerulonephritis of Lohlein.

As the renal lesion progresses erythrocytic and granular casts appear in the

* Many patients with acute SLE develop transitory urinary abnormalities and a rise in the blood non protein nitrogen. These patients do not necessarily have lupus nephritis. This can only be diagnosed clinically when the urinary abnormalities persist.

urine of most patients, and epithelial cell casts, fatty casts and oval fat bodies in the urine of some. renal function decreases, azotemia increases, and the clinical manifestations of renal involvement such as nocturia, polyuria and thirst make their appearance. From our experience we suspect that—if they live long enough—almost all patients with progressive lupus nephritis will pass through an edematous stage of nephritis associated with hypoalbuminemia, hypercholesterolemia and much proteinuria. When this nephrotic syndrome appears the typical face rash of SLE may have disappeared and is usually absent once severe renal disease is established. In other patients ill with SLE as we have mentioned above the nephrotic syndrome may be the presenting manifestation of the disease. The diagnosis of SLE may be overlooked because the better known symptoms and signs of SLE may be absent or minimal when edema develops. Usually a carefully taken history establishes the presence of symptoms of SLE in the immediate or remote past. Presumably lupus nephritis is the cause of the nephrotic syndrome in adults in a significant proportion of cases and the exact diagnosis is best made by finding the characteristic histologic picture by renal biopsy.

In this form of the nephrotic syndrome spontaneous or induced diuresis with rapid clearing of water logging is not commonly seen and the edema usually persists for months. Usually the patient's disease slides imperceptibly from the edematous phase into a slowly or more rapidly progressive chronic renal failure. During the edematous phase there may be histologic evidence of either membranous or membranous and proliferative changes in the glomerular tuft and epithelial crescents may be found. The features more peculiar to lupus nephritis are usually present at this stage. Tubular degeneration is evident and fatty changes are demonstrable with special stains. Interstitial edema and mild fibrosis are common and the vessels of the kidney may contain fibrinoid. At this stage of the illness the kidney may be prone to infection and secondary involvement with inflammatory diseases such as pyelonephritis may be evident clinically and histologically. Progression to chronic glomerulonephritis with contraction of the kidney is rare and hyalinization of the glomeruli is unusual. The glomeruli become atrophic or dilated but severe tubular atrophy is rare.

As proteinuria decreases and casts appear in increasing numbers, the tests of renal function become most abnormal. Clinical and laboratory

or during an acute exacerbation of SLE with chronic renal failure and in many cases death is in chronic renal failure and in many cases death is in chronic renal failure.

At the end the kidney may be indistinguishable from that of chronic renal failure.

chronic glomerulonephritis of the common type and microscopically little or no evidence of the lesions typical of lupus nephritis may be found

One other facet of lupus nephritis remains to be discussed. In a few cases the disease may run a fulminating course (pseudo nephrotic syndrome). The glomeruli are severely damaged from the outset. Although a brief history of other symptoms of SLE may be elicited the onset may be sudden. The patient is admitted with much protein in the urine and appears to have the nephrotic syndrome. However the serum cholesterol level is low. In our experience this pseudo nephrotic picture was usually complicated by the development of other evidence of acute SLE such as abdominal crises and myocarditis. After a short stormy illness the patient dies in renal failure. The cause is not difficult to find. Renal function has been compromised by a most extensive and active glomerular disease in which widespread local necrosis, fibrinoid change, karyorrhexis, 'hematoxylin bodies' and hyaline thrombi occupy the stage. Severe tubular damage and interstitial edema, fibrosis and inflammation complete the picture.

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BIBLIOGRAPHY

- 1 ADOLIS, T. A clinical classification of Bright's Disease. *JAMA* 83: 163, 1925.
- 2 ADOLIS, T. *Glomerular nephritis: Diagnosis and treatment*. New York: The McGraw-Hill Company, 1952.
- 3 ALLEN, A. C. *The Kidney: Medical and Surgical Diseases*. New York: Grune & Stratton, 1951.
- 4 ALLEN, A. C. Clinicopathologic meaning of the nephrotic syndrome. *Am J Med* 18: 277, 1955.
- 5 ANGEVINE, D. M. Structure and function of normal connective tissue. *Transactions of the First Conference on Connective Tissues*. *J. Microsc. Jr. Foundation* 13: 1950.

- 11 ALTSCHULE M D A rare type of acute thrombocytopenic purpura Widespread formation of platelet thrombi in capillaries New England J Med 227 477 1942
- 7 ALTSCHULER C H AND ARCEVINE D M Histochemical studies on the pathogenesis of fibrinoid Am J Path 25 1061 1949
- 8 BAEHR G Renal complications of endocarditis Tr A Am Physicians 46 87 1931
- 11 BAEHR G KLEMPERER P AND SCHIFFRIN A A diffuse disease of the peripheral circulation (usually associated with lupus erythematosus and endocarditis) Tr A Am Physicians 50 139 1935
- 10 BAEHR G KLEMPERER P AND SCHIFFRIN A An acute febrile anemia and thrombocytopenic purpura with diffuse platelet thromboses of capillaries and arterioles Tr A Am Physicians 51 43 1936
- 11 BAEHR G AND POLLACK A D Disseminated lupus erythematosus and diffuse scleroderma JAMA 134 1169 1947
- 12 BAGGENSTOSS A H Visceral lesions in disseminated lupus erythematosus Proc Staff Meet Mayo Clin 27: 412 1952
- 13 BAGGENSTOSS A H AND ROSENBERG E J Visceral lesions associated with chronic infectious (rheumatoid) arthritis Arch Path 35 503 1943
- 1
- 15 BARBER H W A case of acute lupus erythematosus Brit J Dermat 21 366 1916
- 16 BARBER H W Lupus erythematosus associated with streptococcal infection of the tonsil Brit J Dermat 31 186 1919
- 17 BARONDESS J A Thrombotic thrombocytopenic purpura Review of the literature and report of three cases Am J Med 13 291 1952
- 18 BEIGELMAN P W Variants of the platelet thrombotic syndrome and their relationship to disseminated lupus JAMA Arch Path 51 313 1951
- 19 BELL E T Renal Diseases Ed 2 Philadelphia Lea and Febiger 1930
- 2
- 21 BERNARDI A AND POLLACK A D A study of the effect of vascular lesions on the clinical course of the disease JAMA Arch Path 51 313 1951
- 22 BEN ASHER S Recurrent acute lupus erythematosus at remission with onset of a case which has survived 23 years after onset of systemic manifestations Ann Int Med 34 243 1951
- 23 BEN ASHER S AND POLLACK A D A study of the effect of vascular lesions on the clinical course of the disease JAMA Arch Path 51 313 1951
- 24 BIRNBAUM M AND POLLACK A D A study of the effect of vascular lesions on the clinical course of the disease JAMA Arch Path 51 313 1951
- 25 BERMAN L VALLROD A R GOODMAN B L AND POLLACK A D A study of the effect of vascular lesions on the clinical course of the disease JAMA Arch Path 51 313 1951
- 26 BEYANS M Pathology of scleroderma with special reference to the changes in the gastrointestinal tract Am J Path 21 25 1945
- 27 BIETT T Traité de médecine des maladies de la peau by Cazeneuve A and Schedel H E Paris 1828 # 336
- 28 BJØRNEBOE M BRUN C GORMSEY H IVERSEN P AND RAASCHOU F The nephrotic syndrome II The effect of corticotrophin (ACTH) Acta Med Scandinav Supp 266: 219 1952
- 29 BLANKENHORN M A AND KNOWLES H C Periarthritis nodosa: recognition and treatment JAMA Arch Path 41 887 1954

- 31 BOLLET A J, SAGAL S, AND BLUM J J Treatment of systemic lupus erythematosus with prednisone and prednisolone JAMA 159: 1501, 1955
- 32 BOOTH, E, MURHEAD, E C, AND MONTGOMERY P O B The fibrinoid of renal cortical necrosis due to the Schwartzman reaction Evidence for its origin from smooth muscle JAMA Arch Path 61: 169 1956
- 33 BOSSAK F T, AND ADLERSBERG D The nephrotic syndrome: attempt at classification by clinical and biochemical criteria Clin Res Proc 3: 139 1955
- 34 BOYD W A Textbook of Pathology Philadelphia, Lea and Febiger 1953
- 35 BRENNER J J, IFF W A AND HOCHSTEIN E Lupus erythematosus disseminatus sine lupo with the nephrotic syndrome Am J Med 5: 288 1948
- 36 BROOKS H G Lupus erythematosus and tuberculosis Brit J Dermat 7: 72 1895
- 37 BROWN T MCP, WICHELHAUSEN R H, MERCHANT W R AND ROBINSON L B Antigen-antibody mechanism in rheumatic diseases Am J Med Sci 221: 618 1931
- 38 BRUNSON J G, AND DAVIS R L Systemic fibrinoid diseases Arch Path 60: 593 1955
- 39 BRUNSON J G, GAMBLE C N AND THOMAS L Morphologic changes in rabbits following the intravenous administration of meningococcal toxin I The effects produced in young and in mature animals by a single injection Am J Path 31: 489 1955
- 40 BRUNSON J G, THOMAS L AND GAMBLE C N Morphologic changes in rabbits following the intravenous administration of meningococcal toxin II Two appropriately spaced injections: the role of fibrinoid in the generalized Schwartzman reaction Am J Path, 31: 655 1955
- 41 BRUNSTING L A Systemic lupus erythematosus N Dakota J Med 7: 311 1954
- 42 BRUNSTING L A, SLOTTUM C H AND DUDOCK J W Effects of cortisone in acute disseminated lupus erythematosus JAMA Arch Dermat & Syph 63: 29 1951
- 43 P W C Editorial Thrombotic thrombocytopenic purpura Ann Int Med 33: 739 1950
- 44 CANTAROW A AND TRUMER M Clinical Biochemistry Ed 5 Philadelphia W B Saunders Co 1955
- 45 CUREY H A, HANFFY A M AND HOWARD J I The effect of adrenocorticotrophic hormone (ACTH) and cortisone on the course of disseminated lupus erythematosus and periarteritis nodosa Bull Johns Hopkins Hosp 87: 125 1950
- 46 Case records of the Massachusetts General Hospital Case 35301 New England J Med 247: 133 1952
- 47 CURRY I Case report to Dermatological Society of London Brit J Dermat 9: 325 1897
- 48 CAZENAVE A Annales des Maladies de la Peau 3: 295 1851 Quoted by Ormsby O S and Montgomery H Diseases of the Skin Ed 7 Philadelphia Lea and Febiger 1918
- 49 CAZENAVE A AND CHAMUSSET J M Traite Elementaire des Maladies de la Peau 8th ed Paris Bailliere 1853
- 50 CAZENAVE A AND SCHERRELL H I Manuel Pratique des Maladies de la Peau 3rd ed Paris 1838
- 51 CHURCH J, AND GORISHMAN I Phase microscope studies of renal glomeruli—glomerular deposits of hyaline substances Am J Path 29: 199 1953
- 52 CITRON K M Renal impairment in sarcoidosis with special reference to nephrocalcinosis Postgrad Med J 31: 516 1955
- 53 CHASTY A Les recherches sur l'etiology du lupus erythemateux depuis 20 ans Ann Dermat et Syph 7: 465 1926
- 54 COHN S ANDERSON I AND BAUER W Length of life and cause of death in rheumatoid arthritis Ann Rheum Dis 12: 323 1953
- 55 COHEN H AND CADMAN I F H The natural history of lupus erythematosus and its modification by cortisone and corticotrophin (ACTH) Lancet 2: 305 1953
- 56 CLE L R Periarteritis nodosa Report of a case with characteristic urinary sediment JAMA 149: 1619 1952
- 57 COVENS, P Experimental hyaline disease and its similarity to disseminated lupus erythematosus J Lab and Clin Med 47: 444 1956

- 58 CONWAY, E J Microdiffusion Analysis and Volumetric Error London, Crosby Lockwood & Son Ltd, 1950
- 59 COOMBS, R R A, MOURANT, A E, AND RACE, R R · New test for detection of weak and "incomplete" Rh agglutinins *Lancet*, 2: 15, 1945
- 60 COOPER, T, STICKNEY, J M, PEASE, G L, AND BENNETT, W. A · Thrombotic thrombocytopenic purpura Confirmation of clinical diagnosis by bone marrow aspiration *Am J Med*, 13 374 1952
- 61 CROCKER, H R Diseases of the Skin Ed 3, Philadelphia, Blakiston, 1953
- 62 DAMMIN, G J, NORA, J R, AND REARDAN, H Hydralazine reaction Case with LE cells antemortem and postmortem, and pulmonary, renal, splenic and muscular lesions of disseminated lupus erythematosus *J Lab & Clin Med*, 46 806, 1955
- 63 DAUGHERTY, G W, AND BIGGENDROSS, A H Syndrome characterized by glomerulonephritis and arthritis Libman-Sacks disease with predominately renal involvement *Arch Int Med*, 85: 900 1950
- 64 DAVSON J, BALL, J, AND PLATT, R The kidney in periarthritis nodosa *Quart J Med*, 17: 175 1948
- 65 DONIZALSKI, C A, AND MORCAY, V C · Dermatomyositis diagnostic features and therapeutic pitfalls *Am J Med*, 19. 370 1955
- 66 DUBOIS E L The effect of the LE cell test on the clinical picture of systemic lupus erythematosus *Ann Int Med*, 38 1265, 1953
- 67 DUBOIS E L, COMMONS, R H, STARR, P, STEIN, C S, JR, AND MORRISON, R Corticotropin and cortisone treatment for systemic lupus erythematosus *JAMA* 149 995, 1952
- 68 DUSTAN, H P, TAYLOR R D, CONCORAN, A G, AND PAGE, I H Rheumatic and febrile syndrome during prolonged hydralazine treatment *JAMA*, 154: 23 1954
- 69 EHRLICH, W E Nature of the collagen diseases *Am Heart J*, 43: 121, 1952
- 70 EHRMANN S AND FALKENSTEIN, F Uber lupus erythematosodes *Arch f Dermat u Syph* 141. 408 1922
- 71 ELKINTON, J R, HUNT, A D, JR, GODFREY, L McCROY, W W, ROGERSON, A G, AND STOKES, J, JR Effects of pituitary adrenocorticotrophic hormone (ACTH) therapy, *JAMA*, 141: 1273 1949
- 72 ELLIS A Natural history of Bright's disease Clinical, histological and experimental observations I Nephritis *Lancet*, 1 1, 1942
- 73 ELLIS F A, AND BERESTOV, E S Lupus erythematosus associated with pregnancy and menopause *Arch Dermat & Syph*, 65 170 1952
- 74 ENGMAN M G, JR Early acute lupus erythematosus *Arch Dermat & Syph*, 35: 685, 1937
- 75 ENTICKNAF, J B, AND JOINER, C L Bright's disease An attempt at a statistical assessment of the classification proposed by Filis *Brit Med J*, 1: 1016, 1953
- 76 ERICHSEN, J Practical observations on some of the more important special diseases of the skin *Lond Med Gaz*, 36: 121, 1845
- 77 FAHEY, J L, LEONARD, E, CHUNG, J, AND GOODMAN, G Wegener's granulomatosis *Am J Med*, 17: 168, 1954
- 78 FISHER, A M Hypertension and Nephritis 5 ed Philadelphia Lea & Febiger 1954
- 79 FOX R A Disseminated lupus erythematosus—in allergic disease? *Arch Path*, 36: 311, 1913
- 80 FRIEDICH, C T The LE cell phenomenon in rheumatoid arthritis Master's Thesis, Graduate School, University of Minnesota
- 81 FRIEDLANDER D The aetiology of lupus erythematosus with especial reference to tuberculosis and a report of thirteen cases tested by the Moro reaction *J Cutan Dis*, 29: 417, 1911
- 82 FRIEDMAN, I A, SICKLEY, J F, POSAE R M, BLACK, A, REEDER P S, KATZ, E, BRONSKY, D, HARTZ W, AND FRIEDICH, C The LE phenomenon in rheumatoid arthritis To be published

- 83 FUCHS C H Referred to by Viel F Jadasohns Handbuch der Haut und Geschlechtskrankheiten Bd X Teil 1 Berlin Springer 1931
- 84 GARDNER D The Schonlein Henoch syndrome (anaphylactoid purpura) Quart J Med 17 95 1948
- 85 GALE J C Electron microscope studies of collagen from normal and diseased tissues Am J Path 27 455 1951
- 86 GALLOWAY J AND MACLEOD J M H Erythema multiforme and lupus erythematosus, their relationship to general toxemia Brit J Dermat 15 81 1907
- 87 GENNERICH W Uber die Aetologie des Lupus Erythematodes Arch f dermat u Syph, 135 181 1921
- 88 GERSH I Application in pathology of method of fixation by freezing and drying of tissues Bull Internat A M Mus 28 179 1948
- 89 GERSH I Ground substance and the plasticity of connective tissues Harvey Lect 45 211 1949-1950
- 90 GINZLER J M AND FOX T T Disseminated lupus erythematosus a cutaneous manifestation of a systemic disease (Libman-Sacks) Arch Int Med 65 26 1940
- 91 GODMAN G C AND CHUNG J Wegener's granulomatosis Pathology and review of the literature A M A Arch Path 58 533 1954
- 92 GOECKERMAN W H Lupus erythematosus as a systemic disease JAMA 80 542 1923
- 93 GOECKERMAN W H AND MONTGOMERY H Lupus erythematosus an evaluation of histopathologic examinations Arch Dermat & Syph 25 304 1932
- 94 GOTTE R H The pathology of progressive systemic sclerosis (generalized scleroderma) with special reference to the changes in the viscera Clinical Proceedings 4 337 1945
- 95 GOLD H C Role of streptomides and penicillin in the pathogenesis of systemic lupus erythematosus Lancet 1 268 1951
- 96 GOLD S C An hypothesis concerning the etiology of systemic lupus erythematosus Brit J Dermat 65 43 1963
- 97 GOLD S C AND GOWING N J Systemic lupus erythematosus a clinical and pathological study Quart J Med 22 457 1953
- 98 GOLDBERG W AND CHASTOT H Hypertension and Hypertensive Disease New York The Commonwealth Fund 1944
- 99 GORE I Disseminated arteriolar and capillary platelet thrombosis A morphologic study of its histogenesis Am J Path 16 155 1950
- 100 GOULD R O Sterol metabolism and its control Symposium on Atherosclerosis National Academy of Sciences 153 1950
- 101 GRAFFIN J W TAYLOR C B AND HARRIS C M A clinical and pathologic study of disseminated lupus erythematosus M Clin North America 33 79 1949
- 102 GRIFFITH G C AND VITALI L Acute and subacute disseminated lupus erythematosus correlation of clinical and postmortem findings in eighteen cases Circulation 3 492 1951
- 103 GROSS L The cardiac lesions in Libman-Sacks disease with a consideration of its relation to acute diffuse lupus erythematosus Am J Path 16 375 1910
- 104 GLETT B AND LAUFER A Further cytochemical studies in systemic lupus erythematosus A M A Arch Path 57 201 1951
- 105 GUNNETT A Ist der Lupus erythematodes ein tuberkulid? Munch med Wchnschr, 50 378 1903
- 106 HALLOPEAU M Case report in Letter from Paris by Wickman L Brit J Dermat., 41 123 1892
- 107 HAMBURGER J GODDÉ-JOLLY D PEAN V AND ZAMBROWSKI S Les néphrites malignes avec lupus érythémateux aigu J d'Urologie 56: 261 1950
- 108 HARGRAVES M M Production *in vitro* of the I.E. cell phenomenon use of normal bone marrow elements and blood plasma from patients with acute disseminated lupus erythematosus Proc Staff Meet Mayo Clin 24 231 1949

- 109 HARGRAVES M M RICHMOND H AND MORTON R Presentation of two bone marrow elements the Tart cell and the LE cell Proc Staff Meet Mayo Clin, 23 20 1948
- 110 HARVEY A M SHILLMAN L L TULLY P A CONLEY C I AND SCHLOSSER E H Systemic lupus erythematosus review of the literature and clinical analysis of 138 cases Medicine 33 291 1954
- 111 HASERICK J R Effect of cortisone and corticotropin on prognosis of systemic lupus erythematosus Arch Dermat & Syph 68: 714 1953
- 112 HASERICK J R Modern concepts of systemic lupus erythematosus a review of 176 cases J Chron Dis 1 317 1955
- 113 HASERICK J R CORCORAN V C AND DUSTAN H ACTH and cortisone in acute crises of systemic lupus erythematosus J A M A 146 643 1951
- 114 HASERICK J R AND LONG R Systemic lupus erythematosus preceded by false positive serologic tests for syphilis presentation of five cases Ann Int Med 37 550 1952
- 115 HEBRA I Ztsch der k k Ges der Aerzte in Wien 1 40 1845
- 116 HEBRA F AND LEFINGER V Atlas der Hautkrankheiten Braumuller Wien 1856
- 117 HEBRA F AND RAPON M K On diseases of the skin including the exanthemata Vol 6 Translated and ed by Warren Tidy London The New Sydenham Society 1875
- 118 HELLER B I JACOBSON S E AND HAMMARSTEN J I The effect of cortisone in glomerulonephritis and the nephropathy of disseminated lupus erythematosus J Lab & Clin Med 37 133 1951
- 119 HENN M J PARKIN T W HARGRAVES M M AND ODEL H M Acute systemic lupus erythematosus syndrome from hydralazine hydrochloride A M A Arch Int Med 95 857 1955
- 120 HILLMANN W KUBITS J H AND SCHLITZ H R Zichten met jout of I L phenomenon Ned tsohr geneesk 99 490 1950
- 121 HILLER A Practical Clinical Chemistry Springfield Ill Charles C Thomas 1953
- 122 JADASSOHN J Lupus erythematosodes in Mirschel F Handb uch der Hautkrankheiten Vol 3 Vienna Alfred Holder 1901
- 123 JADASSOHN J Dermatologie Wien Weilmann 1939
- 124 JAHIEL R AND JAHIEL R Local organ hypersensitivity to autogenous antigens experimental production of pneumonitis J Allergy 21 107 1950
- 125 JANEWAY C A In discussion of paper by Rich V R Tr V Am Phys 64 260 1951
- 126 JARCHO S a series of autopsies
- 127 JESPAR R of lupus erythematosus disseminatus Ann Int Med 38 111 1954
- 128 JONES D B AND JORING W F Glomerular thrombosis Am J Path 27 841 1951
- 129 JOSKE R A AND JORING W F The I E Cell phenomenon in active chronic viral hepatitis Lancet 2 477 1955
- 130 KATSER I H Specificity of perisplenic fibrosis of the spleen in disseminated lupus erythematosus Bull Johns Hopkins Hosp 71 31 1942
- 131 KAMPMEIER R H Vascular diseases due to hypersensitivity so-called diffuse collagen disease in Practit 1 113 1950
- 132 KAPOSI M K Neue Beitr ge zur Kenntniss des Lupus erythematosus Arch f Dermat u Syph 4 36 1872
- 133 KARK R M AND MUEHRCKE R C Biology of kidneys in lupus erythematosus Lancet 1: 1047
- 134 K
- Investigation 34 344 1955
- 135 KARK R M MUEHRCKE R C PIRANI C L AND POLLAK V F The clinical and renal biopsy Ann Int Med 43 807 1955
- 136 KEIL H Relationship between lupus erythematosus and tuberculosis a critical review based on observations at necropsy Arch Dermat & Syph 28 760 1933

- 191 MONTGOMERY H. AND MCCRIGHT, W. E. Disseminate lupus erythematosus Arch Dermat & Syph 60 356 1919
- 192 MONTGOMERY, P. O. B. AND MURHEAD F. L. Fibrinoid and hyaline—a differentiation according to characteristics Am J Path 32: 613 1936
- 193 MOOK W. H. WEISS R. S. AND BROMBERG L. K. Lupus erythematosus disseminatus Arch Dermat & Syph 24 786 1931
- 194 MOULTON III I. AND CIARK E. Viremia in acute hemolytic anemia and in autoagglutination Arch Int Med 89: 270 1932
- 195 MOORE H. C. AND SHEEHAN H. I. The kidney in dermatoma Lancet I 68 1932
- 196 MOORE J. L. AND LUTZ W. H. The natural history of systemic lupus erythematosus—an approach to its study through biologic false-positive reactors J Chron Dis 1 297 1955
- 197 MOCROWITZ E. An acute febrile pleocytomic anemia with hyaline thrombosis of the terminal arterioles and capillaries An unusual disease Arch Int Med 36 89 1925
- 198 MONAT H. Z. AND MORE R. H. The nature and origin of fibrinoid Am J Path 32 611 1936
- 199 MUEHRCKE R. C. KARK R. M. AND PIRANI C. I. Technique of percutaneous kidney biopsy in the prone position J Urol 74 267 1955
- 200 MUEHRCKE R. C. KARK R. M. AND PIRANI C. L. Biopsy of the kidney in the diagnosis and management of renal disease New England J Med 253 537 1955
- 201 MUEHRCKE R. C. KARK R. M. PIRANI C. I. AND FOLLAN V. L. The natural history of "lupus nephritis" Clin Res Proc 3 139 1955
- 202 MUEHRCKE R. C. KARK R. M. PIRANI C. I. FOLKES V. E. AND STICK I. F. The histological and clinical evolution of lupus nephritis Ann Rheum Dis 14 371 1955
- 203 MUEHRCKE R. C. KARK R. M. PIRANI C. I. AND SCHOFENBERGER J. A. Serial kidney biopsy studies in patients with the nephrotic syndrome J Lab & Clin Med 44 901 1954
- 204 MURHEAD F. CRANE G. AND HILL J. M. Diffuse platelet thrombosis with thrombocytopenia and hemolytic anemia (thrombotic thrombocytopenic purpura) Am J Clin Path 18: 523 1918
- 205 NELIGAN J. M. Atlas of Cutaneous Diseases Dublin Tannin and Co 1853
- 206 NEUMANN F. Beitrage zur Kenntnis des Lupus erythematosus Wien med Wochenschr 9: 613 1863
- 207 NEUMANN E. Die Picrocarminfärbung und ihre Anwendung auf die Entzündungslehre Arch f Mikr Anat 25 130 1880
- 208 ORCIZZO M. A. Lupus erythematosus cell reaction—its morphology and specificity Ann Rheum Dis 14: 414 1955
- 209 O'LEARY P. Discussion on paper by Biehr and Pollack J A M A 134: 1173 1917
- 210 OLIVER J. MACDOWELL M. AND LEE Y. C. Cellular mechanism of protein metabolism in the nephron I. The structural aspects of proteinuria: tubular absorption droplet formation and the disposal of proteins J Exp Med 99: 359 1954
- 211 OLIVER J. STRAUSS W. KRITCHNER N. LEE Y. C. DICKERMAN H. W. AND CHENOT F. Histochemical characteristics of absorption droplets in the nephron J Histochem & Cytochem 3: 277 1955
- 212 ORRISON J. I. Morphology of thrombotic thrombocytopenic purpura with demonstration of aneurysms Am J Path 28: 129 1942
- 213 O'LEARY W. On a form of purpura associated with articular gastro-intestinal and renal symptoms New York Medical Journal 48: 675 1888
- 214 O'LEARY W. On the visceral complications of erythema exultans multiforme Am J Med Sci 110: 629 1835
- 215 O'LEARY W. The visceral lesions of the erythema group Brit J Dermat., 12 227 1900
- 216 O'LEARY W. On the visceral manifestations of the erythema group of skin diseases Tr A Am Phys 18 599 1903

- experimentally induced and renal lesions produced by anaphylactic hypersensitivity. *Bull Johns Hopkins Hosp* 87: 549 1950
- 211 RICHARDSON B, BATHURST M, BENNETT I L, JR, COCHRAN T H, GRIFFITH I C and McCANN D C. The effect of ACTH and cortisone upon experimental glomerulonephritis. *Tr Am Soc Med* 61: 957 1951
- 212 RICHARDSON B and GORRY J F. Experimental anaphylactic lesions of coronary arteries of the rat - type commonly associated with rheumatic fever and disseminated lupus erythematosus. *Bull Johns Hopkins Hosp* 81: 312 1947
- 213 RICHARDSON D C. The effects of collagen disease treated with corticoids. *Brit Med J* 2: 77 1951
- 214 RICHARDSON C I, SPINER C I and BLACK R J. Renal involvement in progressive multiple sclerosis. *Clin Rheumatol* 4: 70 1956
- 215 RICHARDSON C I and GOLDWELL L C. Vascular lesions of a disseminated lupus erythematosus. *M Clin North America* 19: 333 1953
- 216 RICHARDSON C I and HILLBURY D M. A disseminated lupus erythematosus - stem cell. *Ann Int Med* 12: 91 1953
- 217 RICHARDSON C I and HILLBURY D M. Lupus erythematosus and ovarian function - observations upon the relation of the two. *Ann Int Med* 21: 1077 1944
- 218 RICHARDSON W and WYLLIE B B. Systemic lupus erythematosus - review of the literature. *J Clin Pathol* 23: 139 1953
- 219 ROBERTSON J C and GRYNBERG J T. The plethysmograph - an experimental and clinical study of plethysmography in relation to respiration, health and disease. *Arch Int Med* 9: 281 1917
- 220 RYAN M H, WENZEL F W, DEER R, SIMLAK R J, GORDON D, THIE J J, RAYZIN D S M and MARRAS G F. Liver function in relation to possible abnormality of the plethysmograph in relation to arthritis. *Ann Rheum Dis* 14: 193 1955
- 221 SALAMON H A. The effect of blood transfusions on the kidney function of the patient with lupus erythematosus. *Acta Med Scandinavica* 131: 337 1948
- 222 SATHI O. Personal communication 1956
- 223 SATHI O. The role of the streptococcus - the etiology of peripheral lupus erythematosus in the rheumatoid group of the rheumatoid arthritis. *J Mign M* 1: 36 277 1957
- 224 SATHI O and SCHLES S S. Simple and accurate method for determination of chloride in the urine. *J Biol Chem* 140: 89 1941
- 225 SATHI O. F. Book of refractions on telescopic refractive elements. *Ann Int Med* 19: 8 1953
- 226 SATHI O and BALS H. Lupus erythematosus - a clinical study of acute and chronic. *Br J Dermatol* 14: 36 1957
- 227 SATHI O, NATHAN H, SWANER A I and MORGAN M. S. Relation of systemic lupus erythematosus to the appearance after valvular disease (aproximal) the rays. *JAMA* 155: 1477 1944
- 228 SHANK R F and HALLAND C I. Modified method for quantitative determination of plethysmography in the rat. *J Biol Chem* 142: 131 1946
- 229 SHERMAN M A and LIMBORSKY B. Disseminated lupus erythematosus - a study of the effects of corticoids. *Arch Int Med* 90: 90 1952
- 230 SHERMAN M C and STURROCK D D. Clinical and laboratory investigation of proteinuria and nephritis. *Arch Int Med* 32: 277 1953
- 231 SHERMAN M C. The effects of corticoids in the treatment of lupus erythematosus. *Br J Dermatol* 19: 71 1957
- 232 SHERMAN M C. Iron, botulinum toxin, and purpura. *Internat Med* 19: 11 1957
- 233 SHERMAN M C. Iron, botulinum toxin, and purpura. *Internat Med* 19: 11 1957
- 234 SHERMAN M C. Iron, botulinum toxin, and purpura. *Internat Med* 19: 11 1957
- 235 SHERMAN M C. Iron, botulinum toxin, and purpura. *Internat Med* 19: 11 1957
- 236 SHERMAN M C. Iron, botulinum toxin, and purpura. *Internat Med* 19: 11 1957
- 237 SHERMAN M C. Iron, botulinum toxin, and purpura. *Internat Med* 19: 11 1957
- 238 SHERMAN M C. Iron, botulinum toxin, and purpura. *Internat Med* 19: 11 1957
- 239 SHERMAN M C. Iron, botulinum toxin, and purpura. *Internat Med* 19: 11 1957
- 240 SHERMAN M C. Iron, botulinum toxin, and purpura. *Internat Med* 19: 11 1957
- 241 SHERMAN M C. Iron, botulinum toxin, and purpura. *Internat Med* 19: 11 1957

- 265 SNAPPER I *Kidney trouble in acute lupus erythematosus* in Berglund H and Medes G *The Kidney in Health and Disease* in Contributions by Eminent Authorities Philadelphia Lea and Febiger 1935
- 266 SOFFER L J AND BADER R Corticotropin and cortisone in acute disseminated lupus erythematosus results of long term use J A M A 149 1002 1952
- 267 SOFFER L J ELSTER S K AND HADMERIAN D J Treatment of acute disseminated lupus erythematosus with corticotropin and cortisone A M A Arch Int Med 93 503 1954
- 268 SOFFER L J LEVITT M F AND BAEHR G Use of cortisone and adrenocorticotrophic hormone in acute disseminated lupus erythematosus Arch Int Med 86 5A8 1950
- 269 SOFFER L J LUDELMANN H H AND BRILL G The effect of corticotropin and adrenal steroids on the management of acute disseminated lupus erythematosus Ann New York Acad Sci 61 418 1955
- 270 SPERRY W M AND WEBB M Revision of Schoenheimer Sperry method for cholesterol determination J Biol Chem 187 97, 1950
- 271 SQUIRE J R The nephrotic syndrome Brit Med J 2 1389 1953
- 272 STICKNEY J M The lesions of the kidneys in disseminated lupus erythematosus Master of Science Thesis Graduate School of the University of Minnesota 1939
- 273 STICKNEY J M Systemic involvement in disseminated lupus erythematosus Proc Staff Meet Mayo Clin 15: 680 1940
- 274 STICKNEY J M AND KEITH N M Renal involvement in disseminated lupus erythematosus Arch Int Med 66 843 1940
- 275 STOKES J H Transition sarcoid lupus erythematosus vs angiolupoid Arch Dermat & Syph 32 694 1935
- 276 STOKES J H BEERMAN H AND INGRAHAM N R Jr The lupus erythematosus concept in attempt at integration Am J M Sc 207 510 1944
- 277 STUMPF G Zur Aetiologie des Lupus erythematosus Dermat Weinschr 82 259 1926
- 278 STUMMERS W St C Thrombotic microangiopathy Histological diagnosis during life Lancet 1 592 1956
- 279 STUMMERS W St C AND BARROWCLIFF D F Platelet thrombosis syndrome J Path Bact 63 552 1951
- 280 STUMMERS W St C AND GILFITT R Polyarteritis nodosa associated with malignant hypertension disseminated platelet thrombosis wire loop glomeruli pulmonary alveolotuberculosis and sarcoid like lymphadenopathy A M A Arch Path 52 489 1951
- 281 TALBOTT J H CASTLEMAN B SMITHWICK R H MELVILLE R S AND PECORA L J Renal biopsy studies correlated with renal clearance observations in hypertensive patients treated by radical sympathectomy J Clin Investigation 22: 337 1943
- 282 TALBOTT J H GALL E A CONVOLAZIO W V AND COONAN F S Dermatomyositis with scleroderma calcinosis and renal endarteritis associated with focal cortical necrosis report of case in which condition simulated Addison's disease with comment on metabolic and pathologic studies Arch Int Med 63 476 1939
- 283 TEILUM G Miliary epithelioid cell granulomas in lupus erythematosus disseminatus Acta Path Scandinav 22 73 1915
- 284 TEILUM G Pathogenetic studies on lupus erythematosus disseminatus and related diseases Acta Med Scandinav 123: 126 1916
- 285 TEILUM G Allergic hyperglobulinosis and hyalinosis (paramyloidosis) in reticulo-endothelial system in Boeck's sarcoid and other conditions morphologic immunity reaction Am J Path 24 389 1918
- 286 TEILUM G Hyperglobulinemia periaarterial fibrosis of the spleen and wire loop lesion in disseminated lupus erythematosus in relation to allergic pathogenesis Am J Path
- 287

- 288 THORN C W FORHAM I H IRRAWLEY T I HILL S R JR RICHIE M STAPHELIN D AND WILSON D I The clinical usefulness of ACTH in the corticoid New England J Med 242: 871 1950
- 289 TREMAYNE M J Solar urticaria (polymorphous) with polyarthritis and glomerulonephritis A report of 2 fatal cases New England J Med 211: 751 1934
- 290 TUNLLEY I A The clinical course of systemic lupus erythematosus J A M A 156: 917 1934
- 291 TUNLLEY I A AND HARVEY A M The clinical course of lesser variant lupus erythematosus A variation of Orlow's criteria J Biol Chem 61: 85 47 1919
- 292 VAN SELTAP D D AND NEILL J M The determination of gamma globulin and other globulins in serum by extraction and immunoelectrophoresis J Biol Chem 61: 523 1934
- 293 VOLK H Periarthritis nodosa before and after Lupus erythematosus dermiformis excoriated one Dermat Ztschr 53: 682 1908
- 294 VOPEL R AND HATCH J T A case of scleroderma with LE cells and prolonged remission on corticosteroid therapy Canad Med Assoc J 72: 597 1955
- 295 VORLICKY I J AND KARR R M Serum cholesterol in health and disease Am J Med 14: 67 1953
- 296 WAGNER B M Histological studies of fibrin in metastases and other normal tissue processes Histopathology 5: 63 1953
- 297 WAINSTEIN J AND DAWSON J The renal appearances in the microscopic form of periarthritis nodosa J Pathol Bact 62: 159 1950
- 298 WAKSBERG B H AND MANNES H I The antigenicity of collagen J Immunol 63: 427 1949
- 299 WALLACE D C Diffuse systemic pleurothoracic thromboses (thrombotic thrombocytopenic purpura) with a report of two cases M J A Arch 2: 9 1951
- 300 WILFONG A AND STEIGER P Thrombotic thrombocytopenic purpura: Review of the literature and report of three cases including a fatal case 17: 889 1950
- 301 WILFONG A AND STEIGER P Nephritic and glomerular lesions in rabbits on corticone Arch Path 31: 275 1950
- 302 WILLIAMS III Treatise of Cutaneous Diseases London H B 1841
- 303 WILSON W J I A practical and theoretical treatise on the diagnosis pathology and treatment of diseases of the skin arranged according to a natural system of classification Philadelphia an outline of the anatomy and physiology of the skin London J Clin Path 1847
- 304 WINTHROP M M AND BERNE J W A standardized technique for the blood sedimentation rate Am J Med 23: 109 1957
- 305 WILSON W Q COHEN C CALABRY F AND IZBA F Studies in serum proteins V A preliminary report on the estimation of total protein true albumin total globulin alpha globulin beta globulin and gamma globulin in 10 ml of serum Am J Clin Path 23: 1915
- 306 WIRKIN B AND LEWSON R D Hemostylin bodies associated with allergic angitis and necrosis of lupus erythematosus Arch Path 56: 233 1953
- 307 ZEPH I M Periarthritis nodosa and other forms of necrotizing angitis New England J Med 248: 761 1953

