RENAL DISEASE IN SYSTEMIC LUPUS ERYTHEMATOSUS: CORRELATION OF MORPHOLOGY WITH CLINICAL COURSE

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I, Nicholas Tromp van Diggelen, hereby declare that the work on which this thesis is based is original (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other University.

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INTRODUCTION

Renal involvement has long been known to be a major cause of morbidity in Systemic Lupus Erythematosus (SLE). The classic study by Klemperer et al in 1941 based on autopsy cases[1] and that of Muehrcke et al. in 1957 based on percutaneous renal biopsies[2], form the basis of our modern understanding of lupus nephritis. The importance of this renal involvement as a major cause of mortality in SLE is also well established.[3,4] In a multicentre study of 1103 patients, lupus related organ system involvement, mainly active nephritis, accounted for 31% of the deaths.[5]

The incidence of renal involvement in SLE is variably quoted dependent on the criteria used to define it. Clinically, renal disease is reported in about 50% of patients during the first year after the clinical diagnosis of SLE and in between 45 and 75% of all cases.[2,6,7] Histologically, some degree of morphologic changes are present in between 80 and 100% of patients and this incidence varies considerably with the criteria for renal biopsy.[8,9] Mahajan et al. in 1977 found histologic evidence of renal involvement in 100% of his patients irrespective of clinical renal involvement.[7]

Lupus nephritis has countless morphologic appearances and can mimic many of the known glomerular diseases.[10] When the technique of percutaneous renal biopsy was introduced in the 1950's it became apparent that the glomerular histology of lupus nephritis was extremely pleomorphic.[11] Since then a number of classifications have been proposed and the first

to gain wide acceptance were those of Pollack and Baldwin in 1964 and 1970 respectively.[12,13] These classifications were based on the light microscopic appearances of the glomeruli and divided lesions into three categories: focal proliferative lupus nephritis, diffuse proliferative lupus nephritis and membranous glomerulopathy. These classifications suffered the inherent problem of classifying glomerular lesions on the basis of light microscopic appearences alone without reference to immunofluorescence or electron microscopy and in addition the entity of mesangioproliferative glomerulonephritis was not recognised and was included in the focal proliferative group.

The classification most widely accepted today is that of the World Health Organisation proposed in 1974.[14] On the basis of a large biopsy series studied by light microscopy, immunofluorescence and electron microscopy, five distinct morphologic patterns were distinguished:

WHO CLASS 1 (The renal biopsy is normal by light microscopy, immunofluorescence and electron microscopy)
There is controversy as to whether or not all patients with lupus nephritis have glomerular immune complex deposition, however in a series reported by Morel Maroger, 26% of patients biopsied had no evidence of renal lesions on light microscopy, immunofluorescence or electron microscopy.[9]

WHO CLASS II (Mesangial lupus nephritis)
In this category there is mild or moderate mesangial hypercellularity by light microscopy and peripheral

capillary loops are thin and delicate (Fig. 1). Tubular, interstitial and vascular lesions are typically minimal in these patients. However cases of interstitial lupus nephritis have been described as causing acute renal failure in the presence of only mesangial proliferation within glomeruli.[15]

In class II, immunofluorescence typically reveals deposits of IgG and complement in the mesangium with IgA and IgM less frequently observed.[16]

Electron microscopy reveals mesangial deposits only and capillary basement membranes are normal. Epithelial cells show foot process fusion and villous hyperplasia which is especially prominent in patients with proteinuria.

Clinically there may be no detectable renal abnormality but often there is mild haematuria or proteinuria, generally less than 1g per 24 hours.

<u>WHO CLASS III</u> (Focal proliferative lupus nephritis):

On light microscopy there is a characteristic focal and segmental endocapillary proliferation in less than half of the glomeruli in the biopsy. These endocapillary proliferative changes are superimposed on a diffuse mesangial increase. The segmental proliferative lesions may show segmental necrosis with varying amounts of fibrinoid material admixed with polymorphs and nuclear debris (Fig. 2). Haematoxylin bodies may be found in association with areas of necrosis. These structures stain lilac in haematoxylin-eosin preparations and are usually smaller than nuclei (Fig. 3). They lack a clear border and merge into the surrounding tissues. Ultrastructually they consist of two

main components. The first is a central mass of electron dense granular material apparently of nuclear origin and the second is a surrounding aggregate of vesicles, vacuoles, glycogen particles and cytoplasmic granules. Cohen and Zamboni have described these features at an ultrastructural level and suggested that they are derived from neutrophils.[17]

Areas of focal necrosis of glomeruli generally heal by fibrosis leaving segmental scars and capsular adhesions or global sclerosis.

Immunofluorescence reveals mesangial deposits of IgG, IgM, IgA and C3 and in most cases there are scattered deposits of immunoglobulin in the capillary wall.[8,18] Electron microscopy reveals mesangial deposits in the majority and scattered subendothelial deposits in half the cases. Subepithelial deposits may be seen in approximately 30% of cases.[8]

Clinically almost all patients have proteinuria. Thirty to 60% of patients have the nephrotic syndrome.[19,20] Haematuria is more frequent than in class II patients and some patients may have a decreased creatinine clearence.[20]

<u>WHO CLASS IV</u> (Diffuse proliferative lupus nephritis):

The light microscopic features of WHO class IV are extremely varied. All glomeruli show some degree of endocapillary proliferation which may be segmentally accentuated (Fig. 4). Segmental necrosis with associated nuclear debris and crescent formation are present in approximately 60% of cases and haematoxylin bodies are seen in up to 30% of cases.[16] A

prominent light microscopic feature of this class is marked uniform thickening of some capillary loops with a refractile hyaline quality - the classic wire loop lesion described by Klemperer and Bauer (Fig. 5).[1] Electron microscopy shows that these are composed of predominantly subendothelial deposits (Fig. 6).

There is a subgroup of lesions within WHO class IV where there is widespread mesangial interpositioning giving rise to a double contour or "tramtracking" feature on the methenamine silver stain, with accentuation of the glomerular lobulation. The picture is similar to mesangiocapillary glomerulonephritis and is termed the mesangiocapillary variant of diffuse proliferative lupus nephritis.

Segmental sclerosis and global sclerosis occurs with time in both active lesions and those that have regressed on treatment.[21]

Immunofluorescence reveals diffuse mesangial staining and irregular heavy staining of capilary loops. IgG and C3 are almost always found in this position.[16,22] IgM is the next most frequent immunoglobulin, followed by IgA.

The tubules, interstitium and vessels form an important component of class IV lupus nephritis. There is frequently a heavy interstitial infiltrate of lymphocytes and plasma cells and there may be active tubular damage as evidenced by tubular basement membrane disruption and lymphocytes between tubular epithelial cells (Fig 7). Varying degrees of interstitial fibrosis and tubular atrophy are found. The interstitial infiltrate may be the result of tubular atrophy

secondary to glomerular sclerosis but it may also be due to an immunologically mediated interstitial nephritis following immune complex deposition along tubular basement membranes and peritubular capillaries.[23,24] In addition, anti tubular basement membrane antibodies, producing a linear immunofluorescence along the basement membrane, have been described producing an interstitial nephritis.[25]

Vasculitic lesions may be found in arterioles. This is however an infrequent finding. They usually occur in cases with florid necrotising glomerular lesions but can occur in association with only mild mesangial deposits .[8,26] Electron microscopy in active class IV lupus nephritis reveals deposits in mesangial, subendothelial intramembranous and subepithelial positions. Of these deposits those with the greatest clinical import are subendothelial which are consistently found in active class IV lupus nephritis .[8,9,26] These subendothelial deposits may be extensive and contribute to the wire loop lesions seen on H&E sections (Fig. 6). They may also expand into the lumen of the loop and are then seen as hyaline thrombi on light microscopy.[27] Subepithelial deposits are irregular in size and larger than in the membranous group.

The endothelial cells frequently show aggregates of branching tubular structures similar to myxovirus particles (Fig 8). In a study by Hurd et al. these tubulo-reticular structures were found in 100% of biopsies from SLE patients, five of whom had normal kidneys by light microscopy. These structures were also present in 24 of 113 patients with renal disease other than SLE.[28] Schaff et al. have

demonstrated that the inclusions were not digested by ribonuclease or deoxyribonuclease and appear to consist of phospholipids and acidic glycoproteins, arguing against a viral origin.[29]

Clinically, the majority of class IV patients have evidence of disordered renal function. Proteinuria is frequent with or without the nephrotic syndrome. Baldwin in 1977 reported that 41 of 44 patients with diffuse proliferative lupus nephritis had the nephrotic syndrome, 26 at presentation and 15 during the course of the disease.[26] Haematuria occurs in up to 90% of patients[8,9,20] and renal function tests show a definite decrease in glomerular filtration rate (GFR) in the majority of patients.[16]

An important phenomenon is that of occult diffuse proliferative lupus nephritis. It is possible to have an active diffuse proliferative lupus nephritis in the absence of any measurable abnormality in renal function or urinalysis. Mahajan in 1977 reported clinically normal renal function and urinalysis in 25% of patients with class IV lupus nephritis and subendothelial deposits.[7] In another study by Eiser in 1979, 3 of 13 patients with SLE and normal urinalysis and serum creatinine values had a diffuse proliferative picture on histology with segmental necrosis of glomeruli.[30]

WHO CLASS V (Membranous lupus nephritis)

In this class the light microscopic features are a diffuse uniform thickening of glomerular capillary walls with some degree of mesangial proliferation (Fig. 9). The methenamine silver stain classically shows "spiking" of the basement

membrane (Fig 10).

Typically the tubular and interstitial changes are minimal. Immunofluorescence reveals granular staining for IgG and C3 in almost all cases. IgM is found in the majority but IgA staining is more variable.[16]

Electron microscopy confirms numerous small subepithelial deposits in the majority of capillary loops with overlying foot process fusion (Fig 11). Mesangial deposits are recognised in approximately half of cases. The features of membranous nephritis may be combined with other WHO classes, i.e. classes III and IV.

Clinically, all patients have proteinuria with the nephrotic syndrome, either at presentation or during the course of the disease.[31] Haematuria is found in approximately 50% of patients.

MORPHOLOGIC TRANSFORMATION. Initially it was thought that histologic lesions of the glomeruli remained static during the course of lupus nephritis however when serial renal biopsies were performed, transformation from one class to another was found to be fairly frequent. Appel found transformation in 11 of 56 patients[8], Baldwin in 15 of 88 patients[26] and Mahajan in 14 of 90 patients.[32] Although transformations have occured between all the various subtypes the most frequent transformation is between class III and IV with an incidence of up to 40%.[8,9,26,33,34]

PROGNOSIS AND OUTCOME:

Muerche et al. in 1957 found a survival of less than 10% at 2 years in patients with diffuse proliferative lupus

nephritis treated with low dose steroids.[2] Since that time the survival of patients with diffuse proliferative lupus nephritis has improved. Baldwin in 1970 found a five year survival of 20% for patients with diffuse proliferative lupus nephritis.[13] Morel Maroger in 1975 found a 5 year survival of 75% [9], Appel in 1978 found a 4 year survival of 66% [8], and Cameron in 1979 found a 78% 5 year survival of class IV patients.[20] This improvement has been attributed to the more aggressive use of corticosteroids and immunosuppressive agents.[35] The prognosis of class III is similar to class IV and this is consistent with the view that they represent different degrees of severity of the same disease process. The prognosis of class II and V have long been known to be relatively good. The 4 year survival of a series published by Zweiman in the 1960's was 85% and the prognosis of the two groups has not improved significantly since.[6,8]

The overall increase in survival has tended to blur the former prognostic implications of the different morphologic subtypes of the WHO classification and considerable controversy has arisen over the role of the renal biopsy in predicting outcome. In recent years several authors have not found a good correlation between the WHO class and eventual clinical outcome.[8,20,22] Cameron attributes this to the marked improvement in prognosis of the severe forms of lupus nephritis.[20] Fries, comparing the predictive information provided by the renal biopsy and that of clinical information without benefit of biopsy, has concluded that the total prognostic content was essentially that of the

clinical information alone.[36] Whitting-O'Keefe has concluded that the contribution of the WHO classification to the predictive power of clinical information is not significant.[37] Authors supporting the value of renal biopsy have stressed the importance of a representative biopsy and Corwin et al., using binomial distribution tables, have estimated that 20 glomeruli are required for an accurate estimate of the degree of renal involvement.[38-40] Because of the lack of correlation between the WHO classification and outcome in the many preceding series, several centres have introduced a semiquantitative scoring system to more accurately define the wide variety of histologic changes present in biopsies in SLE and within each WHO class.[41,42] These scoring systems differentiate between active and chronic lesions and vary slightly in the weighting of individual components. All scoring systems are essentially adaptations of that described by Pirani et al. in 1964 .[41] Semiquantitative scoring is useful in avoiding differences in criteria used for defining the major subgroups of the conventional WHO classification and allows for description of transitions between these major subgroups. Another advantage is the inclusion of tubular and interstitial changes which do not form part of the WHO classification.[43]

Whether semiquantitative scoring correlates with outcome in patients with lupus nephritis is controversial.[44] A study by Austin on 72 patients with diffuse proliferative lupus nephritis using semiquantitative scoring showed that patients with activity indices above 12/24 were at

significantly increased risk of endstage renal disease. Chronicity index appeared to have a graded impact on prognosis allowing identification of patients with low, intermediate and high risks of renal failure. The composite activity index was more strongly predictive than individual active features on the biopsy specimen but each individual chronic pathologic variable i.e. glomerular sclerosis, fibrous crescents, tubular atrophy and interstitial fibrosis was associated with an increased risk of endstage renal disease. Particularly striking was the predictive value of tubular atrophy.[42,45] Leaker et al. using a similar scoring system found a significantly worse survival for patients with an activity greater than 9/42 in the diffuse proliferative group. Patients in this group were more likely to be nephrotic, have haematuria, have more clinical relapses, require more immunosupression and to have an increased mortality from all causes.[46]

Due to the considerable controversy surrounding the role of renal biopsy in predicting outcome this study was designed to determine the predictive power of the initial renal biopsy in lupus nephritis.

PATIENTS AND METHODS

Patients were selected for the study on the basis of 1: A diagnosis of Systemic Lupus Erythematosus according to the 1982 revised American Rheumatology Association criteria[47] and 2: An adequate biopsy defined as containing at least six glomeruli. Patients were biopsied at Groote Schuur Hospital during the period 1978 to 1988 and the indications for renal biopsy were clinical based on laboratory results of renal function. Patients were followed between 1 and 120 months with a mean observation period of 34 months. The clinical records were scrutinised and the following parameters were noted at the time of biopsy: age, sex, race, time from diagnosis to biopsy, serum urea, creatinine, creatinine clearence and urinary 24 hour protein.

Using the latest serum urea, creatinine, creatinine clearence and\or 24 hour urinary protein where available, outcome was graded as:

1: An improvement in renal function

2: A stable renal function

3: Deterioration in renal function

4: Patient on dialysis

5: Death due to disease

RENAL HISTOLOGY

Specimens for light microscopy were fixed in 10% phosphate buffered formalin and paraffin embedded tissue was cut at 2u and stained with haematoxylin and eosin, periodic acid - Schiff, methenamine silver and Masson trichrome stains.

Immunofluorescence microscopy was performed on fresh tissue which was cryostat sectioned and incubated at room temperature for 30 minutes with commercial fluoroscein conjugated sheep anti human IgG, IgA, IgM, C3 and fibrinogen. Slides were viewed under UV light.

If there was insufficient tissue for immunofluorescence, immunoperoxidase staining was performed on paraffin embedded tissue. Paraffin sections were de-waxed in xylol and hydrated in graded alcohol. They were digested in pronase for 15 mins at 37C and blocked in 1% hydrogen peroxide and methanol for 1/2 an hour. Undiluted normal swine serum was applied for 10 mins. Primary antibodies were commercially prepared rabbit anti human IgG, IgM, IgA, C3 and fibrinogen. The linking antibody was swine anti rabbit immunoglobulin. Finally commercially prepared horseradish peroxidase and rabbit anti horseradish peroxidase were applied and colour was developed with the substrate diaminobenzidine and the tissue was counterstained with haematoxylin. Immunofluorescence or immunoperoxidase results were graded as 0 (absent), 1, 2 or 3 for IgG, IgA, IgM, C3 and fibrinogen.

ELECTRON MICROSCOPY:

Electron microscopy was performed on all specimens to confirm the light microscopic diagnosis only and was not used to assess activity or chronicity.

Specimens for electron microscopy were fixed in 5% phosphate buffered gluteraldehyde. Secondary fixation was in 1% buffered osmium tetroxide (Palades fixative). Specimens were dehydrated in graded concentrations of acetone. They were block stained in 0,5% uranyl acetate in 80% acetone. Epoxy blocks were sectioned at 300A on a LKB ultratome using a glass knife and stained with lead citrate and uranyl acetate. Sections were viewed with a Hitachi H600 Electron Microscope at 75 KV acceleration voltage.

WHO criteria were used for classifying biopsies into the five WHO classes using a combined assessment of light microscopy, electron microscopy and immunofluorescence findings.

SEMIQUANTITATIVE SCORING:

Biopsies were scored without prior knowledge of the patient's clinical course using a modification of the system reported by Austin.[42] An explanation of the criteria used is as follows:

Glomerular sclerosis:

Global and segmental sclerosis were distinguished separately but combined for purposes of scoring. Less than 25% of glomeruli sclerosed were scored as 1, between 25% and 50% as 2 and greater than 50% as 3.

Crescents:

Fibrous and cellular crescents were scored separately; both partial and circumferential crescents were scored as follows: Crescents in less than 25% of glomeruli as 1, between 25% and 50% as 2 and greater than 50% as 3.

Overall cellularity:

Overall glomerular cellularity was assessed as normal/minimally increased, moderately increased or markedly increased and scored as 1, 2 or 3 respectively.

Endocapillary proliferation:

The presence of segmental or global endocapillary proliferation was scored as follows: less than 25% of glomeruli as 1, between 25% and 50% as 2 and greater than 50% as 3.

Necrosis:

Foci of necrosis with karyorrhexis and fibrinoid material within glomeruli were scored as 1 if present in less than 25% of glomeruli, between 25% and 50% as 2 and greater than 50% as 3.

Hyaline deposits:

Homogeneous eosinophilic thickening along the circumference of the luminal surface of glomerular capillaries constituted the classic wire loop lesion. More extensive eosinophilic hyaline material occupying the lumen of the capillary loops were identified as hyaline thrombi. The presence of either lesion in less than 25% of glomeruli was scored as 1, between 25% and 50% as 2 and greater than 50% as 3.

Haematoxylin bodies:

Haematoxylin bodies were rarely encountered within areas of necrosis and were not scored as a separate entity. They were noted as present or absent.

Leucocyte infiltration:

The number of glomeruli containing more than five neutrophils were counted and scored as 1 if less than 25% of the total, between 25% and 50% as 2 and greater than 50% as 3.

Capillary loop patency:

The extent of loss of capillary loop patency due to endocapillary proliferation or areas of necrosis was included because the score was assigned to the activity index rather than the chronicity index. Capillary loop patency for each glomerulus was scored as 1 if greater than 75% of the loops were patent, between 75% and 25% as 2 and less than 25% as 3.

Tubules and interstitium:

Tubular atrophy:

Tubular atrophy was identified as a reduction in number of tubules associated with tubular dilatation or collapse with thickening of tubular basement membranes on the methenamine silver stain. This was scored as follows: less than 10% as 1, between 10 and 50% as 2 and greater than 50% as 3.

Tubular basement membrane damage:

Tubular basement membrane damage was recognised as breaks in the tubular basement membrane on the methenamine silver stain in areas of interstitial infiltration. This was scored as 1 if less than 10% of tubules showed basement membrane damage, between 10% and 50% as 2 and greater than 50% as 3.

Interstitial infiltrate:

The presence of an interstitial infiltrate of lymphocytes and plasma cells was graded as mild, moderate or severe and scored as 1, 2 or 3.

Interstitial oedema:

Interstitial oedema was graded as mild moderate or severe and scored as 1, 2 or 3.

Interstitial fibrosis:

The presence of interstitial fibrosis was graded as mild, moderate or severe and scored as 1, 2 or 3 respectively.

Vasculitis was noted as present or absent but not scored.

ACTIVITY AND CHRONICITY INDICES:

The activity index was defined as the sum of individual scores for all the histologically active lesions listed in table 1. Each parameter was scored from 0 to 3 with a total score of 30.

CHRONICITY INDEX

Chronicity index was defined as the sum of individual scores of all the histologically chronic lesions listed in table 2. Each were scored from 0 to 3 with a total of 12.

STATISTICAL METHODS

The significance of each individual morphologic feature as well as the activity and chronicity indices as predictors of outcome was tested by Pearson's Simple Correlation Method and multiple linear regression.

RESULTS

One hundred and fourteen patients fulfilled the selection criteria. Ninety four were female and 20 were male. Figure 12 shows the age distribution by decades. Ages ranged from 14 to 73 years (mean 31 years; median 35). The majority of patients were in the third and fourth decades. Sixty percent of patients were Coloured females. The time from diagnosis to renal biopsy ranged from 1 to 204 months with a mean of 32 months.

HISTOLOGY:

The distribution of WHO classes is shown in table 3. There were no cases in class I. Seventeen patients (15%) were classified as WHO class II, 21 (18%) as class III, 68 (60%) as class IV and 8 (7%) as class V with 2 patients showing a combination of classes III, IV and V.

Tables 4 and 5 show the frequency of individual histologic features. Cellular crescents were present in 30 biopsies (26%) and fibrous crescents were present in 36 (32%). Sixty three biopsies (55%) showed glomerular hyaline deposits, 40 (35%) showed necrosis of at least one glomerulus, 8 (7%) contained haematoxylin bodies within glomeruli and 60 (53%) biopsies showed at least one glomerulus to contain a significant leucocyte infiltrate. Twenty three biopsies (21%) showed interpositioning in the majority of glomeruli enabling them to be classified as the mesangiocapillary subgroup of WHO class IV.

Ninety one biopsies (80%) showed some evidence of tubular atrophy and in 26 (24%) it was severe. Tubular basement membrane damage by an interstitial infiltrate was present in a total of 64 biopsies (56%) with 88 (77%) showing at least a mild interstitial infiltrate. Vasculitis was present in 3 biopsies.

Activity indices ranged from 2 to 28 and chronicity indices ranged from 0 to 10. Tables 6 and 7 show the distribution of these between the WHO classes. The activity indices have arbitrarily been divided into three groups and the chronictiy indices into four groups.

Table 8 shows the immunohistochemical findings: Immunofluorescence was performed on 66 specimens and immunoperoxidase on 12. IgA was detected in 49 specimens (62%), IgG in 54 (70%) and IgM in 59 (76%). Complement was present in 60 cases (77%) and fibrinogen in 11 (3%). IgA was the predominant immunoglobulin in 15 biopsies (20%).

Sixteen patients, 12 females and 4 males with histologic features of WHO class IV had a normal serum creatinine at the time of biopsy.

OUTCOME:

Forty one patients were lost to follow up following biopsy. A total of 73 patients had sufficient follow up information to assess outcome and figure 13 shows the follow up interval of all patients within each outcome group.

Fifteen patients (21%) showed an improvement in renal function, 15 (21%) showed a stable renal function and 15 (21%) patient's function deteriorated. Seven patients (10%) required dialysis and 21 patients (29%) died. Table 9 shows the outcome of patients within each WHO class. Table 10 illustrates the outcome and the number of cases with activity indices divided arbitrarily into three groups. Table 11 shows the number of cases and the outcome of patients with chronicity indices divided arbitrarily into four groups. Figure 14 shows the range of activity indices and figure 15 shows the range of chronicity indices for each outcome group.

Multiple linear regression analysis of all the histologic variables (table 12) showed that the histology alone contributes only 20% to the prediction of outcome (R Square = 0,20148). Multiple linear regression also shows that histologic parameters either singly or in combination do not correlate significantly with outcome (Significance of F = 0.4243 and Significance of T >0.01).

Analysis by Pearson's Simple Correlation Method (see appendix 1) confirmed the results of multiple linear regression analysis and showed no significant correlation between individual histologic parameters and outcome. There was also no significant correlation between WHO class, activity or chronicty index and outcome.

This statistical test did show a cross correlation to a statistical significance of 0.001 between the presence of each of 12 of the 14 parameters that made up the activity and chronicity index with the exception of interstitial oedema and interstitial infiltrate. The presence of these two parameters did not cross correlate with the presence of the other parameters but did correlate with each other and the presence of tubular basement damage to a statistical significance of 0.001.

DISCUSSION

This study documents the histological features of lupus nephritis in 114 patients seen over a ten year period and examines the correlation between the histology of the initial biopsy and eventual outcome.

The age and sex distribution of the patients is similar to other large series all showing a predominance of females in the third and fourth decades.[7,20,42,46]

The distribution of histology into focal proliferative (including mesngioproliferative), diffuse proliferative and membranous groups is remarkably similar in many reported series (table 13). This study similarly shows the majority of cases (60%) to be in the diffuse proliferative group (WHO class IV) at the time of biopsy. Sixteen of these patients had a normal serum creatinine at the time of biopsy, supporting the observation that clinical markers of renal involvement do not always correlate with the severity of histological features.[7]

Renal biopsies containing six or more glomeruli were considered adequate for this study. Corwin[39] has recommended 20 as the minimum but for most centres this is unrealistic. Other studies have accepted a minimum of six glomeruli as an adequate renal biopsy.[26,42]

Certain problems in the methodology were encountered. In some cases it was difficult to distinguish between pure mesangial proliferation and endocapillary proliferation of glomeruli on light microscopy particularly where compression artefact near the edge of the biopsy caused obliteration of capillary loops. The thickness of the section was important in assessing glomerular cellularity as a thick section led to a false impression of increased cellularity. Normal and minimally increased cellularity were both scored as 1. Tubular and interstitial changes were usually patchy, in particular interstitial infiltrates and tubular atrophy. These changes were scored semiquantitatively using grades of mild, moderate and severe and consistency was difficult when only a small amount of tissue was available.

Light microscopy was performed by one person with the advantage that any errors in interpretation were consistently applied. These difficulties and errors in interpretation could be minimised by consultation with other observers. Pirani has made a systematic test of the reproducibility of semiquantitative scoring in systemic lupus erythematosus. Fifty seven biopsy and autopsy specimens were analysed in 1956 initially and were re-analysed again in 1962 as part of a larger study. Semiquantitative analyses were made on 12 glomerular changes and eight tubular and interstitial changes on both ocasions by two different observers using a grade of 0 to 4. Between the 1956 and 1962 analyses there was a difference in the grade assigned in only 2% of the features analysed. The

reproducability of this system is due in part to the fact that both observers were trained in the same laboratory.[41] Immunoperoxidase appeared to be less sensitive than immunofluorescence and presented problems in interpretation mainly due to background staining of the biopsy.

Electron microscopy was particularly useful in detecting early membranous nephritis and small subendothelial deposits not visible by light microscopy. In some cases, when only sclerosed glomeruli were present, it did not contribute to the diagnosis.

Fourteen histological parameters on light microscopy (tables 1 and 2) were scored semiquantitatively and analysed both singly and in combination as well as combined as an activity and chronicity index to assess the value of histology in predicting outcome. Follow up information was available on seventy three patients. This number is considered sufficient for statistical purposes.

Statistical results show that the initial histology alone does not predict outcome. The squared correlation coefficient (R^2) calculated from multiple linear regression showed that histology alone contributes only 20% to the prediction of outcome. This squared correlation coefficient is a measure of predictability of outcome and is shown in table 12 to be 0,20148 (20%).

Individual histological parameters either singly or in combination do not correlate significantly with outcome. Pearson's Simple Correlation Method did not show a statistcally significant correlation between activity or chronicity index and outcome or between WHO class and outcome. Cameron has found a similar lack of correlation between initial histology and outcome. He found no difference in outcome between two groups of patients, one with a mild grade of histology (WHO classes 1, II and V) and the other with a severe grade of histology (WHO classes III and IV). Of a total of 71 patients there were 10 deaths in the mild group (30 patients) and 9 deaths in the severe group (41 patients). Four patients in the severe group showed complete clinical remission. He attributes the lack of correlation of histology with outcome to transformations of mild lupus nephritis to more severe forms as well as the improvement in prognosis of the severe forms with treatment.[20] Hecht has studied 31 patients with lupus nephritis grading the histology into mild, moderate and severe groups on the basis of the distribution of glomerular changes. His mild group was defined as less than 50% of glomeruli showing endocapillary proliferation, crescents or necrosis. The moderate group showed 50% to 75% of glomeruli involved by these changes and the severe group showed greater than 75% of glomeruli involved. He found that the light microscopic changes of the first biopsy did not correlate with long term outcome.[22] Wallace has found that biopsy patterns of pathology were of no prognostic importance in prognosis in 51 patients biopsied of his large

series of 230 patients with clinical evidence of lupus nephritis.[4] Fries has analysed a series by Baldwin in 1970 in which histology was graded as membranous, focal or diffuse proliferative and demonstrated that the biopsy grade was not significantly associated with death.[36]

If one could generate a theoretical "prognostic factor" for lupus nephritis which would be completely accurate in predicting outcome, this prognostic factor would include several components, of which, according to the statistical analysis in this study, the histology contributes only 20%. The other contributing factors which would need to be considered when generating this prognostic factor would be

1. Whether the histological parameters assessed actually represent valid components of the disease process in the kidney or whether they are non specific.
2. Possible transformations of the initial histology.
3. The potential of severe forms of lupus nephritis to resolve on treatment.
4. Posssible biopsy sampling error.
5. Clinical predictors of outcome.

1. The validity of the histology can be examined by referring to the results of Pearson's Simple Correlation Test where the presence of any one of the fourteen histologic parameters was cross correlated with the presence of any of the others. There was a cross correlation between the presence of twelve of the fourteen histologic parameters with the exception of interstitial oedema and interstitial infiltrate. The fact that these twelve histologic parameters

cross correlate suggests that they are part of the disease process under study. Interstitial oedema and interstitial infiltration do not cross correlate with the other twelve parameters. The presence of either of these parameters only correlated with the presence of the other and the presence of tubular basement membrane damage suggesting that they are are not an integral part of the disease. Both correlate with tubular basement membrane damage and this suggests that they are, at least in part, a consequence of this basement membrane damage.

2. Transformation of the initial histology has been frequently observed in lupus nephritis. Ginzler described a group of 31 patients with mesangioproliferative or focal proliferative glomerulonephritis 11 of whom were rebiopsied because of clinical deterioration. Repeat histology showed progression to diffuse proliferative glomerulonephritis in nine.[48] He suggested that mesangioproliferative, focal and diffuse proliferative nephritis represent stages along a continuum of increasingly severe renal disease in systemic lupus erythematosus.[48] Similarly, Zimmerman described a group of 17 patients with mesangioproliferative or focal proliferative nephritis on initial biopsy, 6 of whom showed clinically progressive disease. Re-biopsy in all six showed progression to diffuse proliferative glomerulonephritis.[34] Baldwin has described progression from focal to diffuse proliferative lupus nephritis in 2 out of 12 patients.[26] Cameron documents a similar progression from mesangioproliferative or focal proliferative to diffuse

proliferative in 5 out of 13 patients who were rebiopsied in his series of 71 patients.[20] It is therefore possible for the initial histology to transform from mild to more severe grades. The histology may also transform from a severe to a milder grade. However, this is only observed in a proportion of cases following treatment, as discussed in item 3. Transformation from a mesangioproliferative or focal proliferative nephritis to a diffuse proliferative nephritis would always increase the activity index because more glomeruli would show endocapillary proliferation, hyaline deposits, cellular crescents and other features of activity. In addition the tubular and interstitial changes observed in diffuse proliferative lupus nephritis would contribute to an increase in activity index. The chronicity index may or may not be increased depending on the degree of glomerulosclerosis, fibrous crescent formation, tubular atrophy and interstitial fibrosis encountered in the subsequent biopsy.

3. An important factor influencing outcome is the potential of severe forms of lupus nephritis to resolve on treatment. This has been the experience of a number of authors. Hecht studied a group of 31 patients with lupus nephritis and graded initial histology into mild, moderate and severe groups on the basis of the number of glomeruli involved by endocapillary proliferation, cellular crescents and necrosis. The mild group was defined as less than 50% of glomeruli involved. The moderate group was defined as

between 50% and 75% of glomeruli involved and the severe group as greater than 75% of glomeruli involved. All patients received prednisone and cyclophosphamide. Seven patients out of a total of 16 in the severe group showed clinical improvement and rebiopsy of all seven patients showed disappearance of the diffuse proliferative lesion with reversion to a residual mesangioproliferative nephritis on light microscopy and disappearance of subendothelial deposits on electron microscopy in four patients.[22]

A study by Baldwin divides the histology of the initial biopsy of 88 patients into mesangioproliferative, focal proliferative, diffuse proliferative and membranous lupus nephritis. All patients received steroids in varied doses depending on the severity of disese. Forty four patients showed a diffuse proliferative nephritis on initial biopsy and serial biopsies were performed on six patients who underwent clinical remission in this group. In all six the subsequent histology showed conversion to a mesangioproliferative glomerulonephritis with glomerulosclerosis. In addition fewer deposits were demonstrated on electron microscopy and immuno-fluorescence.[26]

Cameron studied a group of 71 patients with lupus nephritis dividing the initial histology into four grades. Grade 1 was described as mesangioproliferative glomerulonephritis, grade 2 as membranous nephropathy, grade 3 as focal proliferative nephritis and grade 4 as diffuse proliferative glomerulonephritis. Fifteen patients were classified as grade 4 and were treated with prednisone and azathioprin.

Repeat biopsies were only performed on three patients in grade 4. One showed conversion to a mesangioproliferative nephritis, one converted to a focal proliferative nephritis and one remained a diffuse proliferative nephritis.[20] The changes on biopsy are therefore not static and may vary either towards a more or a less severe grade depending on progression of disease and the effect of treatment. The activity and chronicity index will therefore change depending on at what stage the patient is biopsied during the course of his or her disease.

4. Biopsy sampling error is another factor which must be borne in mind when interpreting renal histology. Lewis has stressed the importance of an adequate biopsy sample especially when assessing focal glomerular lesions. Because of the focal nature of the involvement of glomeruli by the lupus process it is important to consider the statistical significance of the degree of involvement of the renal biopsy compared with that which may actually exist in the kidney. Using an application of the binomial theorem he suggests 20 glomeruli as the minimum for an accurate assessment of the actual extent of glomerular involvement.[38] The statistical outcome that is measured in any study incorporating clinical follow up is dependent on the criteria for distribution into histologic categories; an inadequate biopsy sample could result in a patient with relatively mild glomerular abnormalities being incorrectly categorised into a more severe histologic group, or vice

versa, which would in turn reduce the predictive value of the histology. Experience is also needed in the technique of percutaneous needle biopsy to obtain an adequate sample.

5. Fries argues that clinical markers of renal disease are more important than renal biopsy results in predicting outcome. This fact has been stressed by Fries who analysed data from a study by Baldwin in which 51 patients were divided into groups with focal nephritis (14 patients), menbranous nephritis (14 patients) and diffuse proliferative nephritis (23 patients) on biopsy. In the first group the mortality within one year was 7%, in the second group 14% and in the third, 17%. The same 51 patients were then divided by Fries into clinical classes based on published clinical information as follows: "Mild" represented patients with proteinuria of 2+ or less. "Moderate" was defined as massive proteinuria but a blood urea nitrogen of 25 mg/dl or less and "severe" was defined as a blood urea nitrogen of greater than 25 mg/dl. Using this clinical grading system, no patients died in the mild group (26 patients) within one year. Of 15 in the moderate clinical class three died (20%) within one year. In the severe group four of ten patients (40%) were dead within one year. There was a greater separation of outcome for clinical classes (0%, 20%, 40%) than for biopsy classes (7%, 14%, 17%). The clinical information was significantly associated with death (chi square = 10.5) however biopsy information was not (chi square = 0.78).[36] Whiting O'Keefe has selected the records of 30 patients with lupus nephritis who had a renal biopsy

done and also had a known clinical outcome. Detailed case histories were prepared and randomly chosen cases were given to 197 academic rheumatologists who were asked to estimated the probability of certain future clinical events (worsened serum creatinine, wosened urine protein exretion, renal death and the need for aggressive therapy) without knowledge of the biopsy information. The biopsy information was then supplied and the rheumatologists were were again asked to esimate the probability of the same clinical events. The change in predictive accuracy was calculated for each clinical event. There was no significant change in prediction accuracy for renal death, 24 hour urine protein or serum creatinine. Only the accuracy of predicting whether the patient would receive aggressive treatment was significantly improved by the knowledge of the biopsy results.[37]

CONCLUSION

In contrast to other studies showing a correlation between semiquantitative scoring of serial renal biopsies and outcome ,[42,45,46] this study shows that the histologic information of the initial renal biopsy in patients with lupus nephritis can not be used to predict outcome. It is possible that serial biopsies may be of more value in formulating a histological predictor of outcome as any transformation in histology from a mild to a more severe grade, or vice versa, could be included in the final histologic assessment.

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TABLE 1 : ACTIVITY INDEX

GLOMERULI

Cellular Crescents

Endocapillary Proliferation

Necrosis

Hyaline Deposits

Leucocyte Infiltration

Capillary Loop Obliteration

Glomerular Cellularity

TUBULES AND INTERSTITIUM

Interstitial Infiltrate

Interstitial Oedema

Tubular Basement Membrane Damage

TABLE 2 : CHRONICITY INDEX

GLOMERULI

Glomerular Sclerosis

Fibrous Crescents

TUBULES AND INTERSTITIUM

Interstitial Fibrosis

Tubular Atrophy

TABLE 3 : DISTRIBUTION OF WHO CLASSES

WHO CLASS	NO. CASES	
I	0	
II	17	(15%)
III	21	(18%)
IV	68	(60%)
V	6	(5%)
III & V	1	(1%)
IV & V	1	(1%)

TABLE 4 : FREQUENCY OF GLOMERULAR CHANGES

GLOMERULAR CHANGES	NO. CASES	
Cellular Crescents	30	(26%)
Fibrous Crescents	36	(32%)
Hyaline Deposits	63	(55%)
Segmental Necrosis	40	(35%)
Haematoxyphil Bodies	8	(7%)
Leucocyte Infiltrate	60	(53%)
Interpositioning	23	(21%)

TABLE 5 : FREQUENCY OF TUBULO-INTERSTITIAL CHANGES

TUBULO-INTERSTITIAL CHANGES	NO. CASES	
Tubular Atrophy	91	(80%)
Tubular Basement Membrane Damage	64	(56%)
Interstitial Infiltrate	88	(77%)

TABLE 6 : DISTRIBUTION OF ACTIVITY INDEX FOR EACH WHO CLASS

	W H O				
ACTIVITY INDEX	I	II	III	IV	V
0 - 10	0	17	15	4	7
11 - 20	0	0	6	42	1
21 - 30	0	0	0	22	0

Figures represent numbers of patients

Total = 114

TABLE 7 : DISTRIBUTION OF CHRONICITY INDEX FOR EACH WHO CLASS

	W H O				
CHRONICITY INDEX	I	II	III	IV	V
0 - 3	0	15	10	21	3
4 - 6	0	2	8	24	3
7 - 9	0	0	3	16	2
10 - 12	0	0	0	7	0

Figures represent numbers of patients.

Total = 114

TABLE 8 : IMMUNOHISTOCHEMICAL RESULTS

IMMUNOHISTOCHEMISTRY	NO. CASES	
1gG	54	(70%)
1gA	49	(62%)
1gM	59	(76%)
C3	60	(77%)
Fibrinogen	11	(3%)
1gA > 1gG and 1gM	15	(20%)

Total number of cases = 78

TABLE 9 : OUTCOME OF EACH WHO CLASS

		OUTCOME				
WHO CLASS	**n**	1	2	3	4	5
II	10	3	1	2	0	4
III	14	3	3	2	0	6
IV	45	9	9	10	7	10
V	2	0	1	1	0	0
III & V	1	0	1	0	0	0
IV & V	1	0	0	0	0	1
TOTAL	73	15	15	15	7	21

Outcome: 1 = Improved renal function;

2 = Stable renal function;

3 = Deterioration in renal function;

4 = Patient on dialysis; 5 = Death.

Values represent number of patients

Number of patients followed = 73

TABLE 10 : OUTCOME OF RANGES OF ACTIVITY INDEX

		OUTCOME				
ACTIVITY INDEX	**n**	1	2	3	4	5
0 - 10	25	5	6	4	0	10
11 - 20	34	7	9	7	4	7
21 - 30	14	3	0	4	3	4
TOTAL	73	15	15	15	7	21

Outcome: 1 = Improved renal function; 2 = Stable renal function;
3 = Deterioration in renal function;
4 = Patient on dialysis; 5 = Death.
Number of patients followed = 73.

TABLE 11 : OUTCOME FOR RANGES OF CHRONICITY INDEX

CHRONICITY INDEX	n	OUTCOME				
		1	2	3	4	5
0 - 3	32	8	9	5	3	7
4 - 6	24	2	3	7	2	10
7 - 9	15	5	3	2	1	4
10 - 12	2	0	0	1	1	0
TOTAL	73	15	15	15	7	21

Outcome: 1 = Improved renal function;

2 = Stable renal function;

3 = Deterioration in renal function;

4 = Patient on dialysis; 5 = Death.

Number of patients followed = 73

TABLE 12 : MULTIPLE LINEAR REGRESSION

Variable	B	SE B	Beta	T	Sig T
TUBATHR	-.37368	.36171	-.25798	-1.033	.3058
NECROSP	-8.28063E-03	.01260	-.09946	-.657	.5138
GLOSCLSP	.01679	.01860	.11748	.903	.3705
HYALP	1.183597E-03	6.23877E-03	.03108	.190	.8502
INTEROED	-.34333	.26664	-.22091	-1.288	.2030
FIBCRESP	.02920	.01900	.21196	1.537	.1297
CELCRP	.01837	.02329	.11752	.789	.4334
LEUCP	5.256264E-04	.01042	8.9930E-03	.050	.9599
INTERFIB	.37956	.35752	.17182	1.062	.2928
CAPLOP	3.355020E-04	7.94473E-03	7.7476E-03	.042	.9665
GLOMCELP	-.02488	.01240	-.65763	-2.006	.0495
INTERIN	-.12270	.27520	-.09782	-.446	.6574
TBMD	.54586	.39123	.32462	1.395	.1683
ENDOPRP	.02291	.01311	.57350	1.747	.0859
(Constant)	3.05578	.41416		7.378	.0000

Multiple R	.44886
R Square	.20148
Adjusted R Square	.00873
Standard Error	1.51076

Analysis of Variance

	DF	Sum of Squares	Mean Square
Regression	14	33.40125	2.38580
Residual	58	132.37957	2.28241

F = 1.04530 Signif F = .4243

TABLE 13 : LUPUS NEPHRITIS = DISTRIBUTION OF HISTOLOGY

AUTHOR (Ref)	NO. PATIENTS	HISTOLOGICAL TYPE %		
		FOCAL*	DIFF. PROL.	MEMB.
Sinniah (49)	56	27	60	13
Epstein (50)	47	28	66	6
Zimmerman (34)	43	40	53	7
Morel-Maroger (18)	112	37	55	9
Austin (51)	102	14	70	16
Leaker (45)	135	27	58	15
This study	114	33	60	7

* FOCAL = Focal segmental proliferative and mesangio-proliferative glomerulonephritis.

APPENDIX I

PEARSON'S SIMPLE CORRELATION METHOD

Correlations:	TOTGLOM	CELCR	ENDOPR	NECROS	HYAL	LEUC
TOTGLOM	1.0000	-.1318	.1081	.0972	.1096	-.0357
CELCR	-.1318	1.0000	.1685	.1603	-.0683	.2245
ENDOPR	.1081	.1685	1.0000	.4139**	.6142**	.5608**
NECROS	.0972	.1603	.4139**	1.0000	.2268	.4861**
HYAL	.1096	-.0683	.6142**	.2268	1.0000	.3275*
LEUC	-.0357	.2245	.5608**	.4861**	.3275*	1.0000
CAPLO	.1989	.1682	.6822**	.2522	.4689**	.3890**
GLOMCEL	.0539	.1197	.9059**	.3801**	.6165**	.4639**
INTERIN	.0200	.3292*	.1980	.0097	.3055*	-.0462
INTEROED	-.0314	.3420*	.2644	.0806	.1060	.2467
TBMD	.0229	.3972**	.2486	.1227	.2286	.1639
GLOSCLG	.2061	-.0195	-.0711	-.0130	.0037	-.0684
GLOSCLS	.0185	.1126	.0530	-.1600	.0452	-.0789
FIBCRES	.0916	.2827*	.2038	.1271	.1327	.0894
INTERFIB	.2644	.0832	.0972	.0582	.0411	-.0467
TUBATHR	.1637	.3391*	.3136*	.0891	.2498	.1899
WHO	-.1348	.2436	.5614**	.2478	.4245**	.3362*
COMMENT	-.1984	.0964	-.1763	-.1132	-.1230	-.0446

N of cases: 73 Significance: * - .01 ** - .001

" . " is printed if a coefficient cannot be computed

Correlations:	CAPLO	GLOMCEL	INTERIN	INTEROED	TBMD	GLOSCLG
TOTGLOM	.1989	.0539	.0200	-.0314	.0229	.2061
CELCR	.1682	.1197	.3292*	.3420*	.3972**	-.0195
ENDOPR	.6822**	.9059**	.1980	.2644	.2486	-.0711
NECROS	.2522	.3801**	.0097	.0806	.1227	-.0130
HYAL	.4689**	.6165**	.3055*	.1060	.2286	.0037
LEUC	.3890**	.4639**	-.0462	.2467	.1639	-.0684
CAPLO	1.0000	.6469**	.3498*	.2115	.3859**	.4442**
GLOMCEL	.6469**	1.0000	.2760*	.2748*	.2642	-.0155
INTERIN	.3498*	.2760*	1.0000	.4820**	.7377**	.3672**
INTEROED	.2115	.2748*	.4820**	1.0000	.6248**	.0207
TBMD	.3859**	.2642	.7377**	.6248**	1.0000	.2964*
GLOSCLG	.4442**	-.0155	.3672**	.0207	.2964*	1.0000
GLOSCLS	.0845	.1210	.1609	.0349	.0826	.0404
FIBCRES	.3985**	.2014	.3130*	.3302*	.4528**	.3843**
INTERFIB	.2581	.1144	.3068*	.0128	.3723**	.3160*
TUBATHR	.5426**	.3120*	.6919**	.4848**	.7743**	.4270**
WHO	.4299**	.5285**	.3763**	.1764	.2915*	.2246
COMMENT	-.0951	-.2533	-.0211	-.1355	.0766	.0178

N of cases: 73 Significance: * - .01 ** - .001

" . " is printed if a coefficient cannot be computed

Correlations:	GLOSCLS	FIBCRES	INTERFIB	TUBATHR	WHO	COMMENT
TOTGLOM	.0185	.0916	.2644	.1637	-.1348	-.1984
CELCR	.1126	.2827*	.0832	.3391*	.2436	.0964
ENDOPR	.0530	.2038	.0972	.3136*	.5614**	-.1763
NECROS	-.1600	.1271	.0582	.0891	.2478	-.1132
HYAL	.0452	.1327	.0411	.2498	.4245**	-.1230
LEUC	-.0789	.0894	-.0467	.1899	.3362*	-.0446
CAPLO	.0845	.3985**	.2581	.5426**	.4299**	-.0951
GLOMCEL	.1210	.2014	.1144	.3120*	.5285**	-.2533
INTERIN	.1609	.3130*	.3068*	.6919**	.3763**	-.0211
INTEROED	.0349	.3302*	.0128	.4848**	.1764	-.1355
TBMD	.0826	.4528**	.3723**	.7743**	.2915*	.0766
GLOSCLG	.0404	.3843**	.3160*	.4270**	.2246	.0178
GLOSCLS	1.0000	.3463*	.0977	.1528	.0542	.0730
FIBCRES	.3463*	1.0000	.2674	.5170**	.2401	.1802
INTERFIB	.0977	.2674	1.0000	.5759**	.0670	.1699
TUBATHR	.1528	.5170**	.5759**	1.0000	.3677**	.0395
WHO	.0542	.2401	.0670	.3677**	1.0000	-.0382
COMMENT	.0730	.1802	.1699	.0395	-.0382	1.0000

N of cases: 73 Significance: * - .01 ** - .001

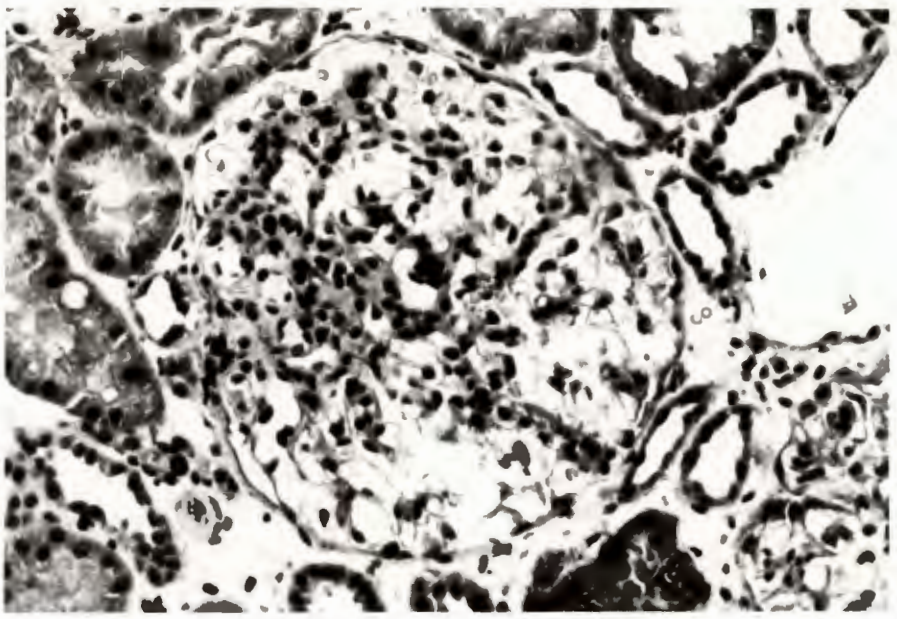
" . " is printed if a coefficient cannot be computed

TOTGLOM = TOTAL NUMBER OF GLOMERULI
CELCR = CELLULAR CRESCENTS
ENDPR = ENDOCAPILLARY PROLIFEREATION
NECROS = NECROSIS
HYAL = HYALINE DEPOSITS
LEUC = LEUCOCYTES
CAPLO = CAPILLARY LOOP OBLITERATION
GLOMCEL = GLOMERULAR CELLULARITY
INTERIN = INTERSTITIAL INFILTRATE
INTEROED = INTERSTITIAL OEDEMA
TBMD = TUBULAR BASEMENT MEMBRANE DAMAGE
GLOSCLG = GLOBAL GLOMERULOSCLEROSIS
GLOSCLS = SEGMENTAL GLOMERULOSCLEROSIS
FIBCRES = FIBROUS CRESCENTS
INTETRFIB = INTERSTITIAL FIBROSIS
TUBATR = TUBULAR ATROPHY
WHO = WHO CLASS
COMMENT = OUTCOME

ILLUSTRATIONS

Fig. 1. WHO class II (Mesangial lupus nephritis). The glomerulus shows a moderate increase in mesangial matrix and cellularity. Capillary loops are thin and delicate. H&E. X150.

Fig. 2. WHO class III (focal proliferative lupus nephritis). There is segmental endocapillary proliferation of the glomerulus with superimposed necrosis and nuclear debris. H&E. X600.



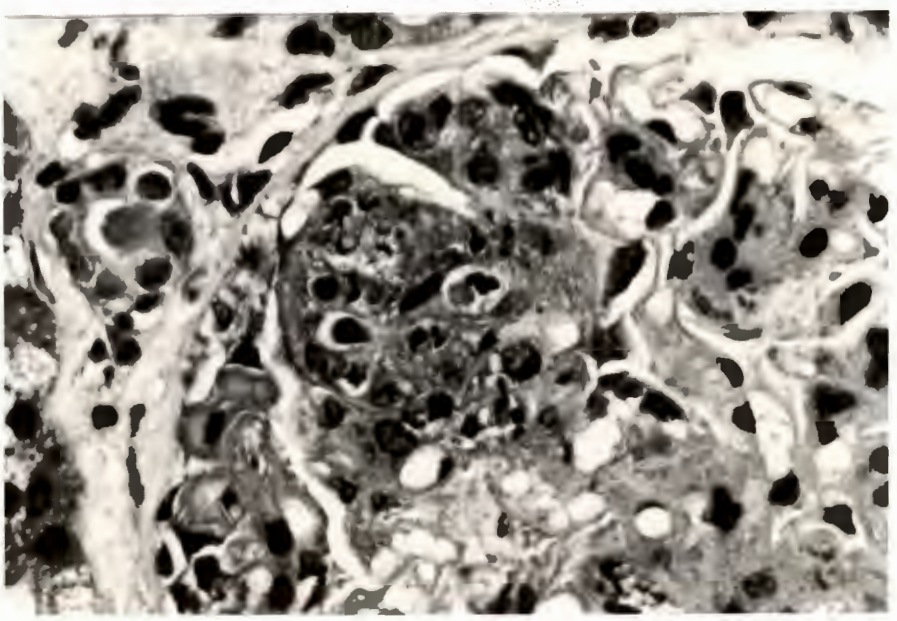
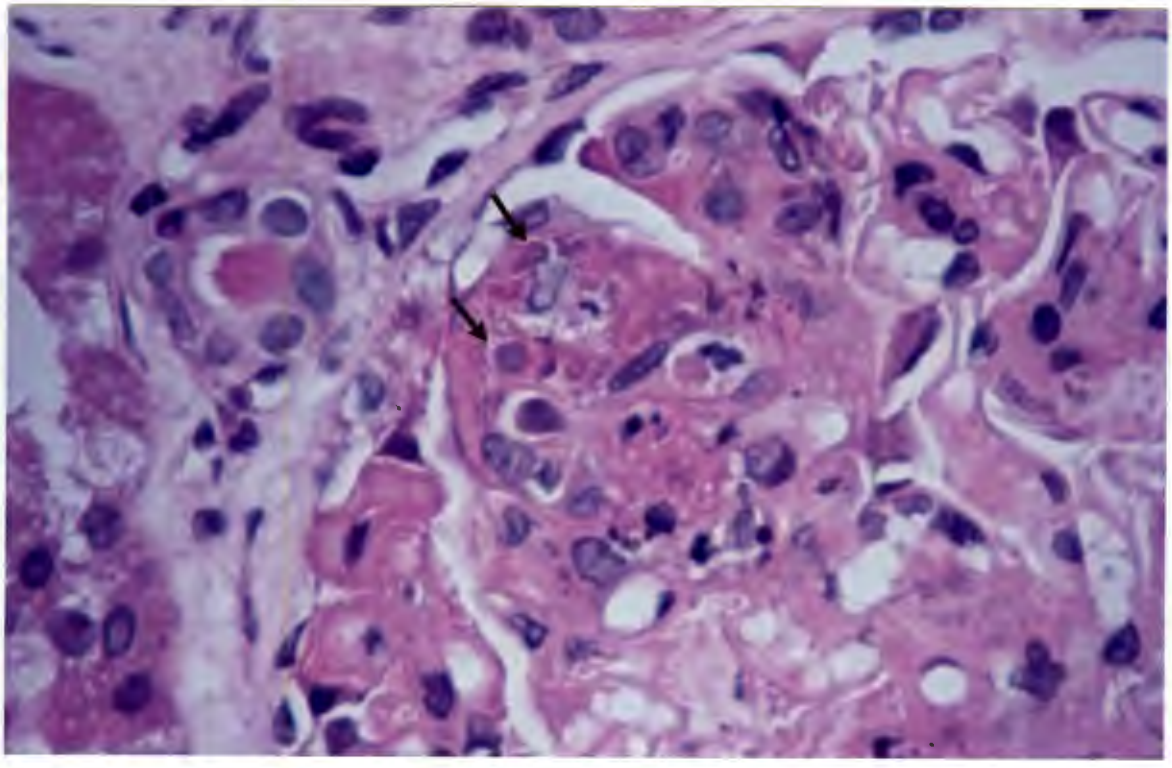


Fig. 3. Haematoxylin bodies are seen as purple flecks within an area of necrosis (arrows). H&E. X800.

Fig. 4. WHO class IV (diffuse proliferative lupus nephritis). Two adjacent glomeruli show endocapillary proliferation with obliteration of capillary loops and a neutrophil infiltrate. The glomerulus on the left shows a cellular crescent. H&E. X150.



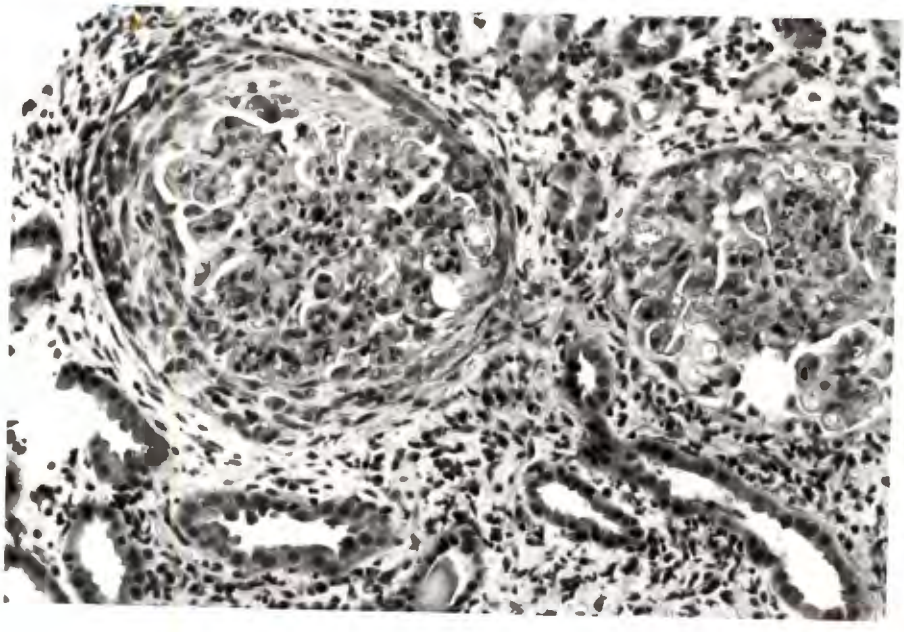


Fig. 5. WHO class IV (diffuse proliferative lupus nephritis) showing marked hyaline thickening of numerous capillary loops. This is the "wire loop" lesion of lupus nephritis. H&E. X600.

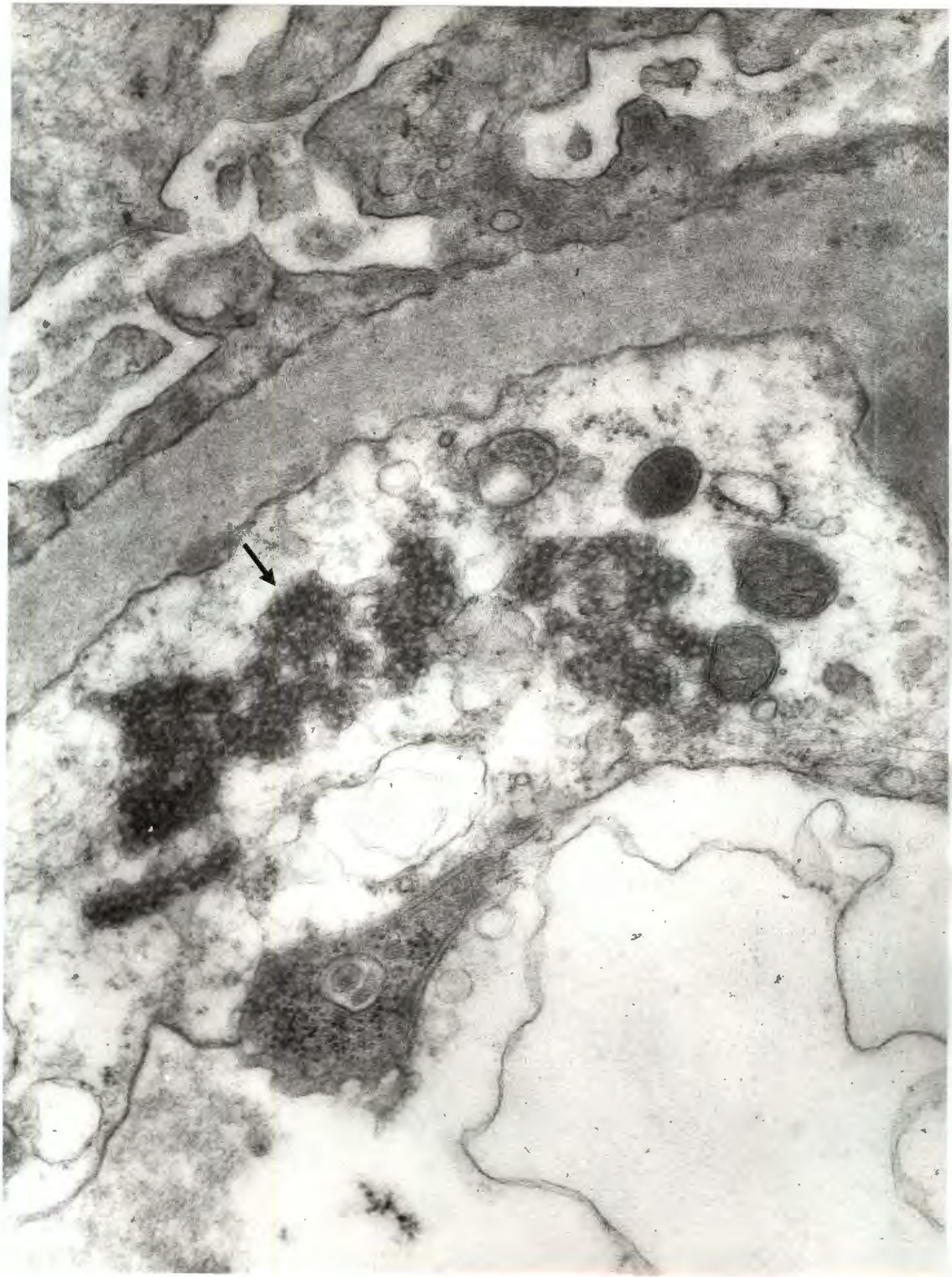


Fig. 9. WHO class V. Capillary loops show diffuse uniform thickening. H&E X600.

Fig. 10. WHO class V. The basement membrane shows "spiking" of the epithelial aspect (arrow). Methenamine silver X600.

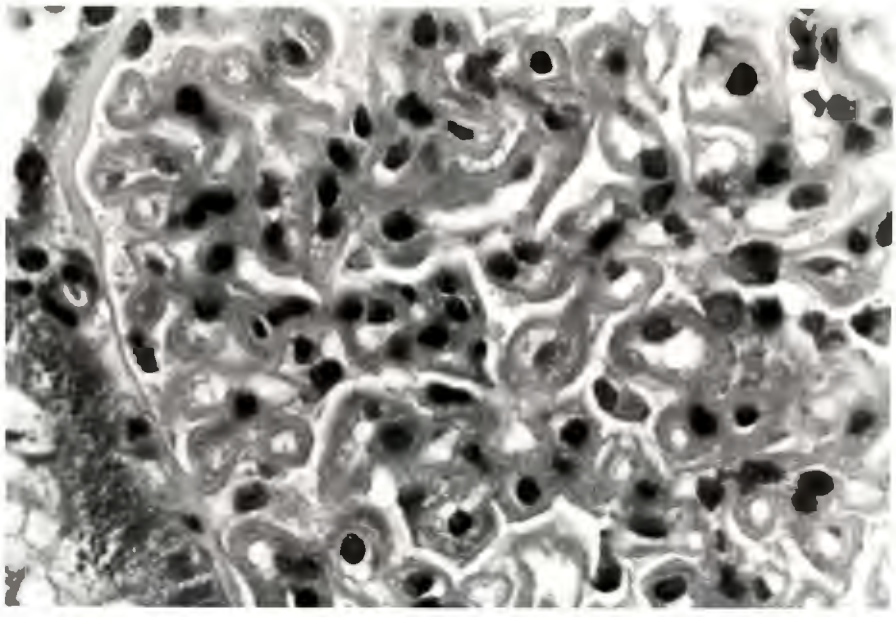


Fig. 11. WHO class V. Electron micrograph shows numerous small subepithelial electron dense deposits with overlying fusion of epithelial foot processes. Lead citrate, uranyl acetate X12000.

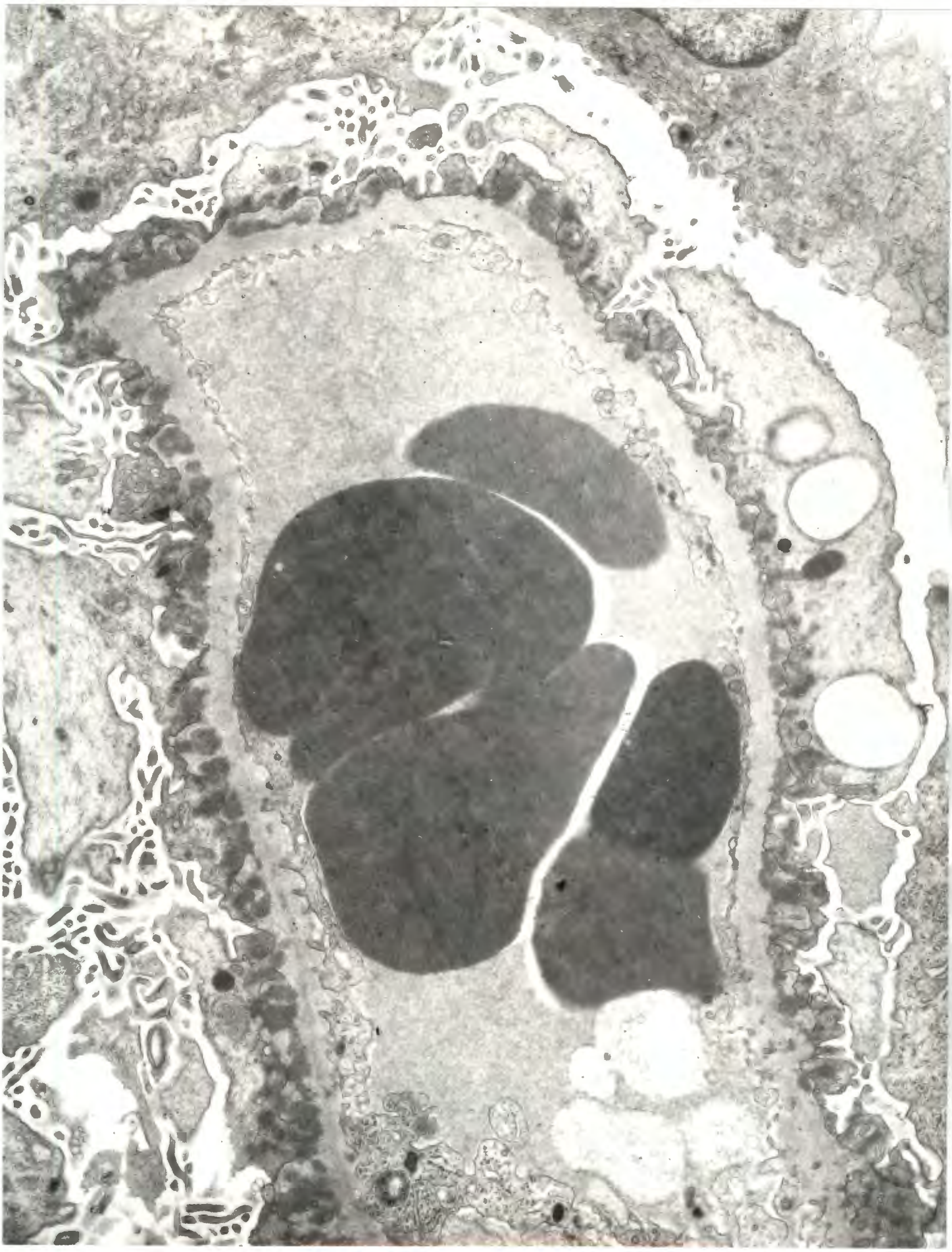


Fig. 12. Age distribution in decades.

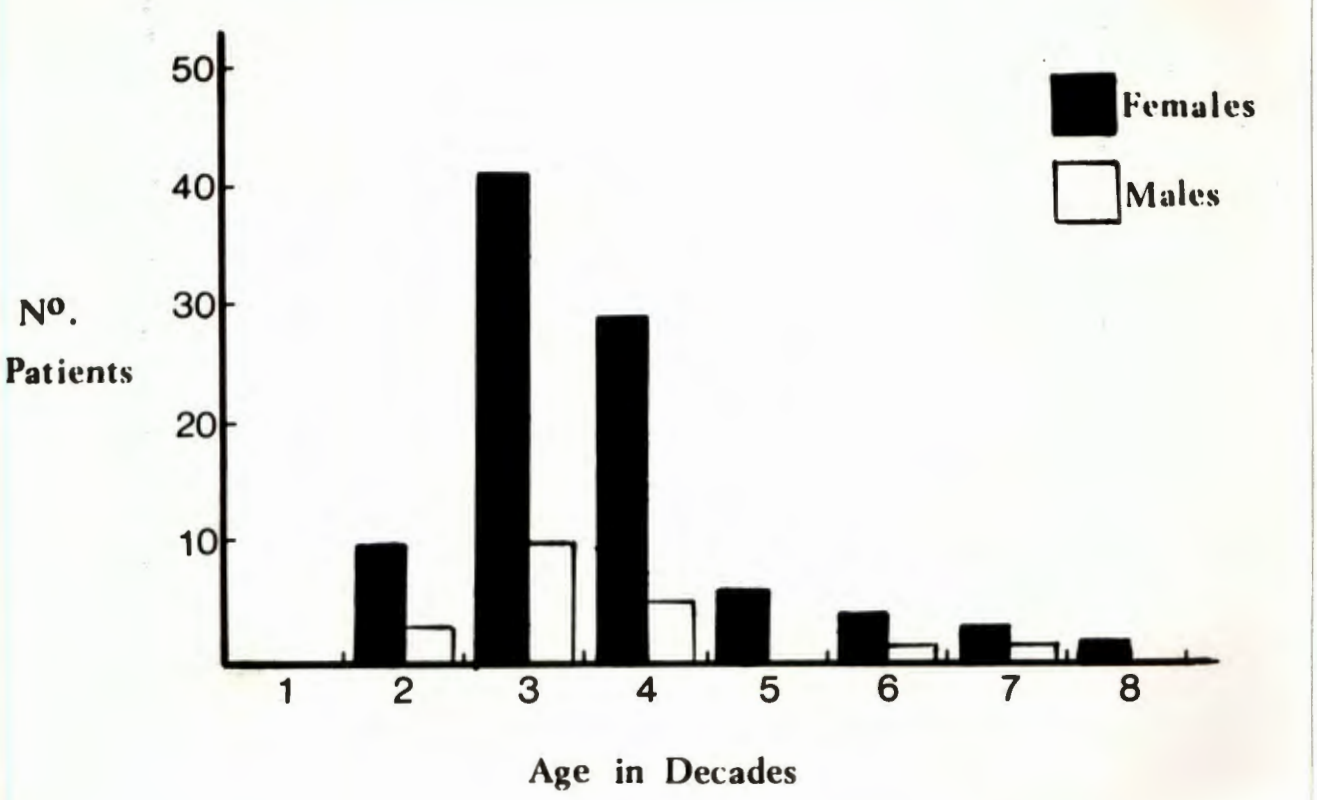

Females
Males
No. Patients
50
40
30
20
10
1
2
3
4
5
6
7
8
Age in Decades

Fig. 13. Follow up interval of all patients within each outcome group. Each dot represents one patient.

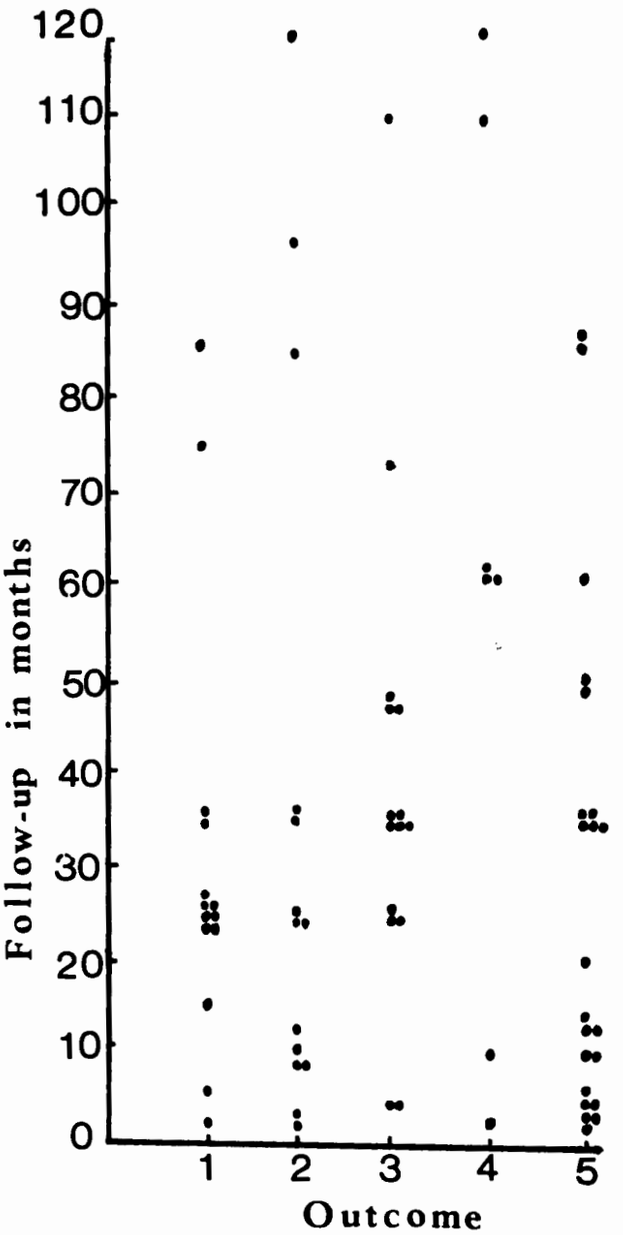
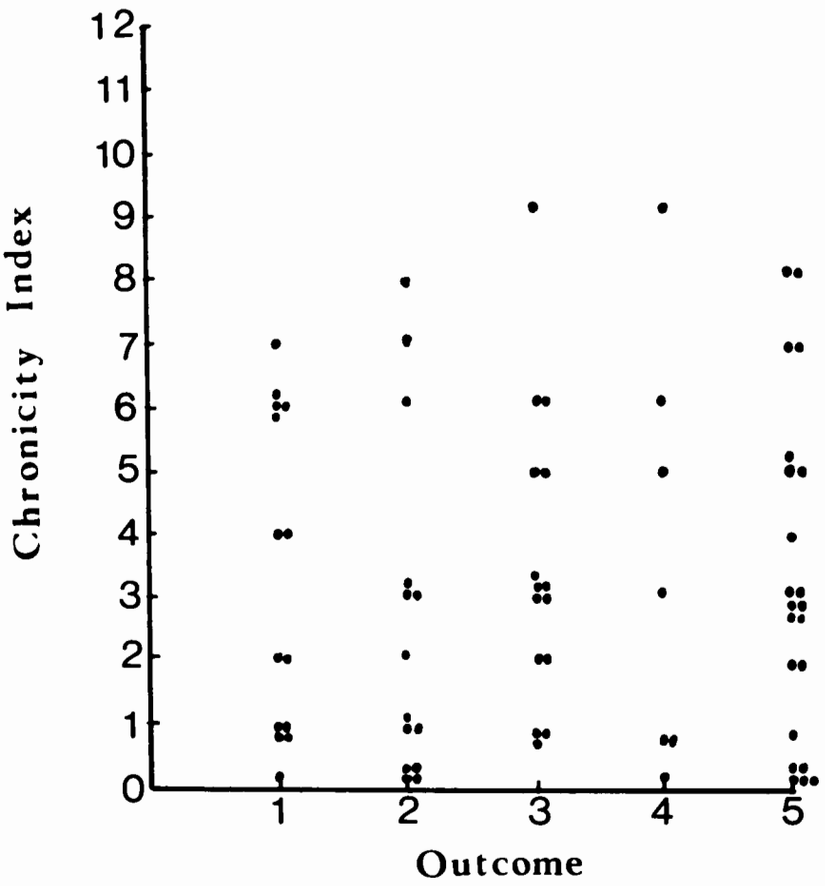

120
110
100
90
80
70
60
50
40
30
20
10
0
Follow-up in months
1
2
3
4
5
Outcome

Fig. 15. Range of chronicity index for each outcome group. Each dot represents one patient.


Chronicity Index
12
11
10
9
8
7
6
5
4
3
2
1
0
1
2
3
4
5
Outcome