
**RAPIDLY PROGRESSIVE
GLOMERULONEPHRITIS AT
GROOTE SCHUUR HOSPITAL**

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The Faculty of Medicine
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for the Degree of Master of Medicine

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ABSTRACT

Rapidly progressive glomerulonephritis (RPGN) is a rare syndrome which occurs as a result of primary renal disease or in association with multi-system disorders. The classification is based on pathogenetic mechanisms and the aetiology and incidence differ in various parts of the world. Despite the diverse aetiology of this syndrome, the presenting clinical features are similar. Laboratory investigations and histology are essential for confirming the diagnosis of RPGN and may also help in confirming a specific aetiology. Therapy and subsequent outcome are dependent on the underlying cause. The prognosis of RPGN is poor despite advances in therapy. The clinical and histological features of RPGN are reviewed.

The aim of this study was to review the clinical and histological features of patients presenting with RPGN. A retrospective study was performed for the period January 1977 to April 1991. The clinical features of 73 patients were reviewed from case notes and the histology was reviewed using stored material.

Groote Schuur Hospital (GSH) serves a heterogeneous community with diseases having both first and third world components. The most common presenting clinical features and urinary findings were non specific in nature. Patients with RPGN secondary to systemic lupus erythematosus or vasculitis tended to present with better renal function than patients with idiopathic RPGN or post infectious RPGN. Serological assays were useful in the

aetiological diagnosis of RPGN, in particular SLE and post infectious glomerulonephritis (PIGN). Histology was essential for the diagnosis of RPGN but the study reflects the difficulty in making a definitive diagnosis of the underlying nephritis on light microscopy.

The mortality or progression to renal failure in the study was high (53%). Thirty three percent of patients with PIGN did not recover renal function, indicating that the disease is not as benign as previously reported. Seventy eight percent of patients with SLE either died from complications of SLE or did not recover renal function. Seventy six percent of patients with idiopathic RPGN and 10% of patients in the vasculitis group failed to recover renal function. The study revealed a unique profile of RPGN. The clinical features were non specific and the biochemical assessment of renal function was not a significant prognostic indicator. Prognosis in patients with greater than 80% crescents was poor, however predicting clinical outcome from histology is inaccurate.

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ABBREVIATIONS

ANCA	-	Anti neutrophil cytoplasmic antibody.
ANF	-	Anti nuclear factor.
CH50	-	Total haemolytic complement.
CI	-	Confidence interval.
CIC	-	Circulating immune complexes.
CRP	-	C reactive protein.
EM	-	Electron microscopy.
ESR	-	Erythrocyte sediment rate.
GBM	-	Glomerular basement membrane.
GA	-	Goodpasture antigen.
GN	-	Glomerulonephritis.
GSH	-	Groote Schuur Hospital.
IDIO	-	Idiopathic glomerulonephritis.
IF	-	Immunofluorescent microscopy.
IL	-	Interleukin.
MAC	-	Membrane attack complex.
MCGN	-	Mesangiocapillary glomerulonephritis.
MHC	-	Major histocompatibility complex.
MPO	-	Myeloperoxidase.
NC	-	Non-collagenous.
OR	-	Odds ratio.
PAF	-	Platelet activating factor.
PAN	-	Polyarteritis nodosa.
PIGN	-	Post infectious glomerulonephritis.
PR3	-	Proteinase 3.
RPGN	-	Rapidly progressive glomerulonephritis.
SMAC	-	Sequential multiple analyser computer.
TNF	-	Tumor necrosis factor.
VASC	-	Vasculitic group.
WG	-	Wegener's granulomatosis.

1.1 INTRODUCTION

Rapidly progressive glomerulonephritis (RPGN), the clinical counterpart of necrotising glomerulonephritis (GN) with crescent formation, is an aggressive condition with a rapid, relentless deterioration of renal function. The term RPGN was first used by Ellis in 1942 (1) and has been associated with "malignant" GN (2), acute necrotising GN (3) and acute anuric GN (4). Currently RPGN is referred to as proliferative GN with crescents (5).

Rapidly progressive glomerulonephritis is an uncommon syndrome, occurring in between 2% and 7% of patients with either primary GN or associated with systemic disease (6). The prevalence of this disease has much geographical variability.

Groote Schuur Hospital (GSH) serves a heterogeneous community consisting of many population groups with diseases having both first and third world components. This study, extending from January 1977 to April 1991, reviews the clinical and histological features of 73 patients with RPGN. The entity was defined as those patients having more than 50% crescents on renal biopsy samples.

1.2 CLASSIFICATION OF RPGN

Rapidly progressive glomerulonephritis is currently best classified according to pathogenetic mechanisms. This includes both the primary glomerulonephritides and those associated with systemic diseases. There are three recognized groups of RPGN:

1) Anti-glomerular basement membrane (GBM) nephritis which accounts for approximately 20% of cases, 2) RPGN associated with immune deposits and 3) Pauci-immune or vasculitic RPGN (6,7). The relative incidence of the latter two forms varies in different series due to lack of consistency in definition.

Approximately two thirds of the patients in the anti-GBM nephritis group have associated pulmonary haemorrhage or Goodpasture's syndrome. The remainder have circulating anti-GBM nephritis only. A small number of patients with idiopathic membranous nephropathy may develop anti-GBM nephritis (8,9). Anti-GBM nephritis has also been described with certain toxins and drugs such as penicillamine (10).

Immune complex induced RPGN may follow infection (Post streptococcal GN and bacterial endocarditis), be associated with a systemic collagen vascular disease (Systemic lupus erythematosus or Henoch Schonlein purpura), or be a component of primary renal disease (Mesangiocapillary GN (MCGN) type 1, II or III or IgA nephropathy). Idiopathic forms of RPGN with immune complexes not associated with MCGN and IgA nephropathy have also been described. The pathogenic role of glomerular immune deposits in idiopathic RPGN is controversial. It has been proposed that these complexes represent non specific IgG trapping in glomeruli damaged by another mechanism and are not adequate to explain glomerular injury sufficient to cause crescent formation (6).

Vasculitic RPGN or pauci immune RPGN can be further subdivided into patients with systemic vasculitis or vasculitis confined to the glomerular capillaries (11,12,13). Serum anti-neutrophil cytoplasmic antibody (ANCA) is a marker and a possible pathogenetic factor in immune mediated tissue injury (14). A positive ANCA has been associated with both idiopathic necrotising and crescentic GN as well as systemic vasculitides, principally microscopic polyarteritis nodosa (PAN) and Wegeners granulomatosis (WG). This finding suggests a relationship between vasculitis and idiopathic RPGN with segmental necrotising glomerular lesions. There is growing evidence that this is a variant of PAN limited to the kidney (15). However not all patients with idiopathic crescentic GN have a positive ANCA or a focal necrotising glomerular lesion. Other conditions, such as IgA nephropathy, may account for this category of patients.

1.3 PATHOGENESIS OF RPGN

The pathogenetic mechanisms mediating glomerular damage in RPGN are not yet fully determined.

1.3.1 Anti-GBM antibody disease

The Goodpasture antigen (GA) has been identified and characterized. It is contained in the non-collagenous domain of the type IV collagen molecule (16). Type IV collagen is a helical chain composed of two alpha 1 chains, one alpha II chain and an alpha III chain arranged in a helix interrupted by two non-collagenous (NC1 and NC2) regions (17). Most evidence suggests that GA is

localized in the NC1 domain of the alpha 3 chain. Anti-GBM antibodies to the GA have been shown to be pathogenic. In approximately 66% of patients they are found on the alveolar as well as the glomerular basement membrane (Goodpasture's syndrome). In the remaining cases, the lung has deposits of weakly pathogenic antibody or they are not bound to the alveolar basement membrane at all. The mechanism of induction of autoimmunity appears to have both genetic and environmental factors. There is a higher incidence in the Maoris in New Zealand (18), while the disease is extremely uncommon in Blacks (19). Anti-GBM antibody is strongly associated with the major histocompatibility complex (MHC) class II antigen HLA- DR2 and DR4. Environmental factors such as hydrocarbon solvents (20), and infection (21) have been associated with anti-GBM disease, but a cause and effect relationship has never been established.

1.3.2 Immune Complex Nephritis

Most glomerulonephritides were previously thought to be due to the deposition of circulating immune complexes (CIC) in the glomerulus. It is difficult to distinguish whether these diseases are related to trapping of pre-formed immune complexes or initiated by reactions of antigen and/or antibody with renal tissue, followed by immuno aggregate formation ("Planted Antigen Theory"). The glomerular reaction to these stimuli is the major factor in determining severity of glomerular damage. The intra-glomerular site of the immune complex formation also determines the severity of glomerular damage; immune complexes in

the subepithelial space may produce a non inflammatory, complement dependant, cell independent membranous glomerular lesion. If similar complexes were in a subendothelial location, with more access to inflammatory cells, a proliferative inflammatory lesion, which is complement or macrophage mediated, may occur. The site and severity of glomerular injury also depends on the biological properties of antigen and antibody, such as size, charge, complement fixation ability and biodegradability (22). In addition, the severity of glomerular damage caused by a specific antigen and antibody depends on the quantity of immune complex deposited (23).

Glomerulonephritis following infection was the first described GN in which immunological mechanisms were implicated. Glomerular injury was thought to be due to the deposition of CIC. The theory that nephritogenic streptococcal antigens act as “planted” antigens for subsequent local immune complex formation is now being favored. The exact antigen has not been characterized, but the role of “endostreptosin” as a possible antigen has been proposed. Genetic susceptibility is an important factor with increased frequency of patients with HLA-DR4 (24,25).

Any of the known histological patterns of GN and considerable change between sequential biopsies in the same patient can occur in patients with SLE. The ongoing autoimmune process of SLE results in deposition of IgG, IgM, IgA and the complement components C3, C4 and C1q. These subendothelial and/or mesangial deposits may result in proliferative nephritis (26,27).

Anti-DNA antibody has been consistently associated with SLE nephritis. There is no direct evidence of a pathogenic role for these antibodies or immune complexes. Glomerulonephritis may be due to direct reactivity of auto-antibodies to antigens of glomerular components. These antigens have not been characterized. Genetic, hormonal and environmental factors may also be important in the development of SLE.

IgA nephropathy and Henoch Schonlein purpura are usually associated with IgA containing immune complexes. These may be formed in response to dietary or environmental antigens (28). Alternatively, non specific polyclonal activation of B cells secreting IgA antibodies that react directly with mesangial antigens may occur.

MCGN is divided into types I, II and III. Type I disease is characterized by subendothelial deposits and has been regarded as an immune complex disease. Type II disease has "dense deposits" within the glomerular basement membrane. The nature of "dense deposits" is unknown; they are associated with C3 but not immunoglobulin deposition. Type III MCGN is similar to type I disease but is characterized by both subepithelial and subendothelial deposits (29).

Considerable progress is being made in the understanding of the pathogenesis of immune-complex GN. The disease process appears to be initiated by multiple immunological mechanisms. If the initiating event is sufficiently severe, progressive renal disease, including crescentic GN, may occur.

1.3.3 Vasculitic Nephritis

The association of ANCA with the vasculitic group of diseases has improved our understanding of this disease process. ANCA reacts with constituents of neutrophil primary granules and monocyte lysosomes (30). Two types have been identified using indirect immunofluorescent microscopy. Cytoplasmic ANCA (C-ANCA) binds a 29 kilo-Dalton molecule found in neutrophil primary granules, which is probably proteinase-3 (31). Perinuclear ANCA (P-ANCA) is an autoantibody to myeloperoxidase, a lysosomal enzyme present in primary granules of neutrophils and monocytes (32). C-ANCA appears to be a highly sensitive marker for WG. P-ANCA is a less sensitive and specific marker and is associated with PAN, Churg Strauss syndrome and idiopathic necrotising and crescentic GN (33).

ANCA may have a pathogenic role in the ANCA associated diseases. It may stimulate neutrophil respiratory burst and degranulation of lysosomal enzymes resulting in degradation of the glomerular basement membrane (34,35). Auto antibodies to proteinase-3 may form immune complexes with antigens released from neutrophils. Resultant activation of the complement system may damage the glomerular vasculature. Immunofluorescence studies do not show immune complexes on the glomerular basement membrane or in the vessel walls. This may be due to rapid clearance of the immune complexes. Lymphocyte responses to antigens deposited in glomeruli produce crescentic GN in experimental models. Auto-antibodies

may be essential for the initiation of injury after which T cells and cytokine production result in further tissue damage (35).

Despite the strong associations between ANCA and vasculitic illness there is as yet no proven disease-specific pathophysiological role for the auto-antibody. The exact role of these auto-antibodies in the pathogenesis of vasculitis awaits elucidation.

Vasculitic nephritis has also been described in association with various drugs including D- penicillamine (36) and hydralazine (37). Although there are no environmental factors consistently present in patients with vasculitis, it is interesting to note that in the study of 25 patients with microscopic polyarteritis reported from Johannesburg, there was a striking association with employment in the gold mining industry (38).

1.3.4 Capillary Wall Injury

The final common pathway in glomerular crescent formation is the disruption of the glomerular capillary wall. This results in a direct communication between the plasma, blood cells and the Bowmans capsule. Injury to the Bowmans capsule and its subsequent healing may result in crescent formation.

Capillary wall injury may involve several mechanisms:

- a) Antibody to GBM in experimental nephritis can result in capillary wall damage in the absence of complement and

inflammatory cells. However, these components are necessary for crescent formation (39).

- b) Terminal pathway activation (C5b to C9, or membrane attack complex (MAC)), produces severe epithelial cell injury, which may be independent of inflammatory cells (40).
- c) The nephritogenicity of activated neutrophils results from the release of proteases as well as free oxygen radicals, especially hydrogen peroxide. Myeloperoxidase catalyses the reaction between hydrogen peroxidase and chloride anions, generating hyperchloride which causes the halogenation of basal lamina components (41). Complement mediates chemotaxis and immune adherence of neutrophils.
- d) Platelets have also been implicated in the mediation of capillary wall damage (42).
- e) Macrophages have an important role in crescent formation (43,44). Their mechanism of glomerular capillary wall damage is uncertain but may be similar to that of the neutrophil, although they lack the myeloperoxidase system. Macrophages are an abundant source of toxic oxygen metabolites. They release neutral proteinases capable of digesting glomerular basement membrane matrix components and they produce a variety of potent inflammatory mediators with chemotactic and vasoactive properties such as platelet activating factor (PAF), thromboxane A2 and leukotrienes. These substances contribute to a breach in the integrity of the glomerular

capillary wall and allow leakage of plasma proteins and clotting factors, including fibrinogen into the urinary space. Macrophages produce a phospholipoprotein tissue factor which activates the extrinsic clotting pathway causing increased glomerular procoagulant activity which precedes fibrin deposition and crescent formation. Macrophages are also found among fibroblasts and parietal epithelial cells in the crescent where they continue to generate signals for cell replication and collagen synthesis (17).

- f) Endothelial cells can be stimulated by interleukin I (IL I) and tumor necrosis factor (TNF) produced by macrophages, as well as by endotoxin, immune complexes and antibodies (17). This results in cellular adhesion molecule expression and fibrin and endothelin production. Certain endothelial cells produce PAF which provides an added stimulus for leukocyte aggregation (42).
- g) Mesangial cells proliferate and hypertrophy in some forms of crescentic nephritis, especially those containing mesangial cell immune deposits such as SLE and Henoch Schonlein purpura. These cells release potent inflammatory mediators including prostaglandins, reactive oxygen species, interleukins, PAF and neutral proteases (17). The exact role of these mediators in this disease process is not known.
- h) Cell mediated immune reactions may be particularly relevant in cases of RPGN where glomerular immunoglobulin deposits

are not seen. It is uncertain whether there is direct T cell mediation and/or T cell participation in macrophage recruitment (43). It seems likely that some form of cell mediated immunity occurs in idiopathic RPGN.

- i) Other factors which may be important in the pathogenesis of RPGN include the development of anti-endothelial cell antibodies and the expression of adhesion molecules which modulate injury of the endothelium.

The mechanisms discussed result in disruption of the capillary wall with formation of crescents containing macrophages, parietal endothelial cells and later fibroblasts. Fibrin deposition in the capillary walls and urinary space is common to all forms of crescentic nephritis (44). Macrophages or injured glomerular cells induce macrophage procoagulant activity resulting in fibrin formation by activation of the extrinsic coagulation pathway. Cellular crescents become fibro-cellular as fibroblast invasion occurs. The stimuli for proliferation of fibroblasts is unknown, but macrophages, platelets and glomerular cell cytokines have been implicated (45). Old fibrous crescents serve as a marker of disease duration.

1.4 AETIOLOGY

The aetiology and incidence of RPGN differs in various parts of the world. A study in Durban reviewed 27 cases from a total of 458 renal biopsies (5.8%) over a seven year period. The results of this study are summarized in the table below (46).

Another third world study from northern India reported on 36 cases of RPGN including both adults and children. Twenty one (58%) had idiopathic RPGN, nine (28%) had PIGN and the remainder comprised a miscellaneous group of diseases (47). The high incidence of diagnosis of idiopathic RPGN cases may be due either to a truly high incidence of this disease or to inadequate or incomplete diagnostic procedures.

	TOTAL	PIGN	IDIO	MCGN	GBM	PAN	MCTD	SLE
BLACK	15(55%)	6(40%)	5(33%)	2(13%)	1(7%)	0(0%)	1(7%)	0(0%)
WHITE	8(30%)	1(12%)	3(38%)	0(0%)	3(38%)	1(12%)	0(0%)	0(0%)
MIXED	4(15%)	1(25%)	1(25%)	1(25%)	0(0%)	0(0%)	0(0%)	1(25%)

PIGN =Post infectious GN.

IDIO =Idiopathic GN.

MCGN =Mesangio capillary GN.

GBM =Anti glomerular basement membrane disease.

PAN =Polyarteritis nodosa.

MCTD =Mixed connective tissue disease.

MIXED =Mixed race and Indians.

The incidence and spectrum of diseases in European and American studies differs from those seen in South Africa and India. The reported incidence of RPGN varies from 2% to 5%. The vasculitic group of RPGN is larger, with WG and microscopic PAN relatively common, and PIGN rare. The incidence of anti-GBM disease varies from 10% to 20%. The differences may be due to a combination of factors which include socio-economic differences, race, referral patterns and geographical variation (6,48-52).

1.5 CLINICAL PRESENTATION

The age of presentation of RPGN is variable. The Durban study mean patient age was 30 years (46). This low figure is probably a reflection of the relatively high incidence of PIGN. European and American studies give reported median ages ranging from 39 to 58 years. This variation reflects both referral patterns and inter area variation (48-51,53-57). In all the series reviewed, males were more commonly affected than females (46-48,50,51,57).

Despite the varying underlying pathogenesis of RPGN, the clinical features are remarkably similar. The symptoms and signs at presentation depend on both the stage of renal disease as well as the primary disease process. Symptoms of idiopathic RPGN and primary renal disease are usually non specific and include malaise and lethargy, upper respiratory tract symptoms, arthralgia and oliguria (46-51,53,54,56,58,59).

Patients with RPGN associated with systemic diseases often present with more specific symptoms. Haemoptysis is present in about 60% of patients with anti-GBM disease, (5,16,17) and approximately 20% of patients with WG (60). Upper respiratory tract symptoms, sinusitis, arthralgia and arthritis, ocular inflammation, headaches and oral ulcers are also common presenting symptoms in WG (61,62). Microscopic PAN usually presents with a long indolent history of a flu-like prodrome, arthralgias and muscular pains. Haemoptysis and a purpuric skin rash are also common presenting features (63-66). Post infectious GN patients may have a history of an upper respiratory tract or skin infections.

SLE patients can present with any of the characteristic signs and symptoms of this disease.

The presenting signs of RPGN, with the exception of pulmonary haemorrhage and signs specific for other primary diseases, are remarkably similar. Hypertension is present in about 60% of patients, but is a less common finding in patients with idiopathic RPGN where it is usually associated with fluid overload. Oedema is present in about 50% of the patients and may be due to either fluid overload or the nephrotic syndrome (46-51,53,54,56,58,59).

1.6 LABORATORY INVESTIGATIONS

Microscopic haematuria, proteinuria and cellular and granular casts are found in most patients. Macroscopic haematuria occurs in about 30% of cases and protein levels exceeding 3.5 grams per 24 hours in urine is present in about 10% to 30% of cases (47,48,51,67,68). Most patients have an elevated serum creatinine level and the creatinine clearance is usually less than 10% of normal (46-48,58,59). Normochromic normocytic anemia is often present and is frequently more profound than that expected for the severity of renal failure. Iron deficiency anemia may be present in anti-GBM disease. A modest rise in ESR is usual but a rate above 100mm in the first hour suggests underlying systemic disease. Thrombocytosis may occur and is considered a non specific feature of acute disease. Albumin is frequently low due to loss in nephrotic syndrome or an acute phase reaction. Alkaline phosphatase may also be raised in acute vasculitic diseases.

The aetiological diagnosis and monitoring of the course of RPGN requires serological investigation. The most important of these are discussed below:

1.6.1 Serum Complement and Circulating Immune Complexes

Rapidly progressive GN can be associated with normal or decreased complement levels (69). Total haemolytic complement (CH50) is used as a screening assay for hypocomplementemia and serial C3 and C4 levels are used for disease monitoring (70).

Circulating immune complexes are usually raised in RPGN associated with immune complex formation. A number of CIC assays are available of which the solid phase C1q binding assay is probably the best.

Conditions in which complement and CIC measurements are of value include:

- a. SLE: Most SLE patients with renal manifestations have low CH50, C3 and C4. A normal C3 is unusual in renal disease (71,72). Rising C3 and C4 is indicative of successful treatment and a falling C3 and C4 may predict impending disease relapse. Circulating immune complexes (CIC) are a useful correlate and predictor of disease activity (73).
- b. PIGN: C3 is usually low and C4 can be decreased. Chronic ongoing infections such as infective endocarditis result in

decreased C3 and C4 levels. CIC levels can be markedly raised.

- c. **Idiopathic vasculitis:** Some vasculitides, not easily classified, have immune complex deposits with high CIC levels and low C3 and C4. Wegeners granulomatosis and PAN have normal complement and CIC levels.
- d. **Idiopathic MCGN:** MCGN types I and III have low CH50, C3 and C4, probably due to classical pathway activation by immune complexes. High CIC levels are present in about half these cases. C3 nephritic factor (Nef), occurring mainly in MCGN type II but also in MCGN type I, results in low CH50 and C3. CIC levels are usually normal.

1.6.2 C Reactive Protein

C reactive protein is often raised in the vasculitic syndromes, especially PAN and WG. Serum levels are a sensitive indicator of infections and are often used to monitor response to treatment. C reactive protein levels may be raised in SLE but they do not correlate well with other non specific indices of inflammation and may be normal in severely affected patients (74,75).

1.6.3 C-ANCA and P-ANCA

C-ANCA and P-ANCA are specific proteins located in neutrophil primary azurophylic granules and peroxidase positive lysosomes of monocytes. The most prevalent ANCA specificities are for proteinase 3 (PR3) and myeloperoxidase (MPO). Less frequently,

auto antibodies against cationic protein 57 (CAP57) elastin and lactoferrin are also detected. ANCA can be detected by indirect immunofluorescent microscopy staining of cytocentrifuged, alcohol fixed granulocytes or HL 60 cells. One of two distinct staining patterns is observed depending on the antigen specificity of ANCA. C-ANCA is seen in patients with ANCA specific for PR3 or CAP57. P-ANCA, caused by ANCA specific for MPO, is the result of redistribution of cationic granules to surround the nucleus during alcohol fixation. ANCA can also be measured by radio-immunoassays and ELISA techniques (33,76). The latter techniques are of value for monitoring the progress of disease activity as they can be quantitated (77-79).

The sensitivity of ANCA for WG varies from 71% to 100% with a specificity of 88% to 100% (77,80-84). These results require cautious interpretation because of the variability of assay methods, the composition of control groups and the criteria for a clinical diagnosis.

P-ANCA is far less specific than C-ANCA in the diagnosis of WG. It is raised in a large variety of conditions with deep organ inflammation. Approximately 80% of patients with P- ANCA have histological evidence of vasculitis including microscopic PAN, systemic vasculitis, idiopathic RPGN, SLE, rheumatoid arthritis and classical PAN. P-ANCA has also been described in "non vasculitic" diseases including primary biliary cirrosis, subacute bacterial endocarditis and broncogenic carcinoma of the lung (85).

1.7 PATHOLOGY

The central finding in RPGN is the presence of crescents within the Bowmans capsule. A crescent is defined as an aggregation of cells, at least two layers deep, which occupy a variable segment of Bowmans capsule, and can extend to obliterate the glomerular tuft (48). The three stages of crescent formation, cellular, fibro-cellular and fibrous, appear to correlate well with the duration of disease (86). Although it was previously thought that macrophages were the major cellular component of crescents (44), current evidence indicates that early crescents contain cells of mixed origin (macrophages +\~30%; neutrophils and epithelial cells +\~50%), fibrin, fibronectin and in some, type IV collagen. Cells are progressively replaced by interstitial type collagen (45,87,88).

1.7.1 Light Microscopy

Epithelial cells and macrophages are the predominant cells in crescents. The epithelial cells are large, elongated and pale with large amounts of glycogen. Mitosis and double nuclei are common. With maturation of the crescent the increase in fibrin gives a characteristic staining pattern. The bundles of fibrin are often surrounded by a zone of paler material which is either modified fibrin or fibrinogen. This is followed by the laying down of collagen bundles which separate the cells. Finally most cells disappear leaving masses of collagen and the easily recognised fibrous crescent on light microscopy.

Glomerular tufts are compressed to a greater or lesser extent, depending on the size of the crescent. In the early stages of crescent formation segment thrombosis and necrosis of the glomerular tuft is seen. Endothelial cells are swollen and there may be proliferation of mesangial cells. Compression of capillaries by the crescent may produce an impression of mesangial enlargement relative to the tuft. The capillary basement membrane often becomes wrinkled, thickened and irregular, and occasionally split. Infiltration of the glomerular tuft with polymorphs is a common feature, particularly in PIGN (51).

Changes specific to the underlying systemic disease may be seen. SLE is associated with various types of GN: The most common variety is diffuse proliferative GN with mesangial proliferation, mesangial deposits and subendothelial deposits. MCGN is characterized by proliferation of mesangial cells, often with segmental or diffuse interpositioning of these cells or their cytoplasm into peripheral capillary loops. There is evidence of increased mesangial matrix synthesis.

Idiopathic RPGN can be divided into two separate histological groups on light microscopy (51). These are necrotising GN with evidence of segmental fibrinoid necrosis of glomeruli and large amounts of fibrin deposition and a proliferative GN characterized by endocapillary proliferation in the glomerular tuft.

Tubular and interstitial damage is variable. Interstitial infiltrates are common in SLE and vasculitic conditions, but less prominent in PIGN. Mononuclear cells predominate and very rarely

eosinophils may predominate. Small and medium sized vessels may demonstrate vasculitis . Arteriolar changes, with narrowing of the lumina by intimal oedema, are common in patients with acute tubular necrosis associated with RPGN. Hypertensive changes are uncommon and usually correlate with a previous history of hypertension. Tubules frequently contain red blood cells and red cell casts.

1.7.2 Immunofluorescent Microscopy

Immunofluorescent microscopy (IF) may aid in the diagnosis of the underlying disease process. Anti-GBM disease has a characteristic diffuse linear staining for IgG along glomerular capillary loops. C3 deposition is commonly seen in a similar pattern (63).

IgG and complement are seen as deposits and correspond to “humps” on electron microscopy in PIGN. Three patterns are observed: The “starry sky” pattern with diffuse and irregular deposits in the glomerular capillary wall, a mesangial pattern characterized by deposits predominantly in the stalk region and the “garland” pattern where deposits are predominantly on the peripheral capillary walls (89).

MCGN types I and III have prominent C3 deposits irregularly outlining the periphery of the lobule, with variable localization in the mesangium. IgG and IgM are found in an inconsistent granular capillary wall and less often mesangial distribution. MCGN type II has C3 heavily deposited in a discontinuous linear pattern (railroad tracks) lining capillary walls, Bowmans capsule and

tubules. There are occasional granular C3 deposits.

IF is less useful in other conditions. In idiopathic RPGN, there may be only small amounts of C3 and IgM in a focal and segmental distribution confined to the mesangium in a few glomeruli (52). Microscopic PAN shows granular deposits of IgG or IgM in a variable pattern when positive for IF. Wegeners granulomatosis usually shows a coarse pattern in all glomeruli when positive for IF. The IF pattern seen in SLE is highly variable, depending on the underlying GN.

1.7.3 Electron Microscopy

In early crescents the epithelial cells are cuboidal with sparse cytoplasmic organelles and are present in small groups joined by intercellular junctions. Groups are separated by narrow channels which communicate with Bowmans space. As the crescent matures the channels are replaced by intercellular material containing collagen. Podocytes of the visceral epithelial cells proliferate but are separated by a narrow gap from the cells of the crescent and have little role in crescent formation (86). Complete rupture of the glomerular basement membrane is occasionally seen. More commonly there is wrinkling of the membrane, and extensive necrosis of both epithelial and endothelial cells with basement membrane preservation (50).

The electron microscopic (EM) finding of subepithelial “humps” is characteristic of PIGN. Deposits can be demonstrated in the subepithelial space, subendothelial or in the mesangium in

SLE (90). Virus-like particles may be seen in the glomeruli in this condition. Anti-GBM disease shows a characteristic change of mottling and widening of the glomerular capillary basement membrane, particularly in the area of the lamina densa (16, 91). Electron microscopy is often essential for the definitive diagnosis of MCGN where splitting of the membrane between the endothelium and the capillary loop is seen. MCGN type I is characterized by subendothelial electron dense deposits and MCGN type III by both subendothelial and subepithelial deposits. The lamina densa of the glomerular basement membrane is transformed into an extremely electron dense character, so-called "dense deposits" in MCGN type II disease.

1.8 TREATMENT

The interpretation of data regarding the benefits of various forms of specific therapy of RPGN is difficult. There are few prospective controlled studies of sufficient size to allow valid conclusions regarding therapeutic options. The relative rarity of RPGN in a single centre has resulted in most trials comparing outcome to historical controls. Validity is compromised by the advances made in controlling progression of renal disease with non-specific therapy such as hypertensive control, dietary measures, improved treatment of infections, fluid management and temporary dialysis techniques. Early diagnosis of disease processes, recognition of milder cases and appreciation of the hazards of severe immunosuppressive therapy may also contribute to the improved results.

Correlation of renal function, histology and prognosis is poor (91,92). The clinical course of patients is often affected by superimposed acute tubular necrosis which resolves independently of therapy. This variable cannot be assessed on the basis of morphological or clinical features. Reports of therapeutic outcome are also biased by the tendency to publish positive rather than negative studies (6).

Corticosteroids, cytotoxic agents, anticoagulants, antithrombotic drugs and plasmapheresis have been used in treatment. Anticoagulant and antithrombotic therapy, initially introduced in 1968, was based on links between the development of crescents and intravascular coagulation, the presence of fibrin and fibrinogen polymers in glomerular lesions and the crescents, the finding of fibrin degradation products in the serum and urine and improvement of lesions with anticoagulants in experimental models (93,94). Anticoagulants and antithrombotic therapy was used in conjunction with steroids and/or immunosuppression in a number of small uncontrolled trials and case reports (95-98). Therapy appeared to be beneficial but the value of anticoagulant and antithrombotic agents was difficult to interpret because of the use of combined therapy. Improvement was not seen in patients with severe reduction in glomerular filtration rate (less than 5 mls per minute). There was an unacceptable rate of haemorrhagic complications and this form of therapy is no longer recommended.

Current therapy for RPGN depends on the underlying aetiology:

- a. **Anti GBM disease:** Uncontrolled trials suggest that treatment with a combination of steroids, immunosuppression and plasmapheresis accelerates the disappearance of circulating anti-GBM antibody and confers additional benefit over steroids and cyclophosphamide alone in the treatment of renal lesions (99,100). Plasmapheresis is most beneficial in patients who are non-oliguric, not on dialysis and have a creatinine less than about 550 $\mu\text{mol/l}$ and should be started early in disease. Plasmapheresis, if instituted, should be intensive and continue for at least two weeks or till the circulating antibodies fall to low or undetectable levels. Immunosuppression with cyclophosphamide and steroids should be continued for at least 8 weeks after the cessation of plasmapheresis to inhibit rebound antibody synthesis. High dose intravenous steroids and cyclophosphamide have not been shown to add benefit in oliguric patients requiring dialysis.

- b. **Idiopathic RPGN:** Steroid pulse therapy given either daily or on alternate days for three successive doses intravenously followed by oral prednisone is probably the current treatment of choice. Dramatic success with responses in oliguric patients and patients on dialysis have been confirmed. The response rate to steroids is probably in the region of 50% to 60%. This figure is a significant improvement compared to historical controls but the influence of other factors previously mentioned have not been accounted for (101-105).

The role of plasmapheresis is controversial; its use is always in conjunction with immunosuppressive therapy. Remission rates appear to be slightly better than with steroids alone, however the difference is not significant (106,107,108,109).

Idiopathic RPGN with evidence of vasculitis and a positive ANCA should probably be treated as microscopic PAN or WG (see below).

- c. Vasculitis (WG, microscopic PAN and idiopathic RPGN with vasculitis): These are often treated with high dose intravenous steroids, followed by oral steroids in combination with either daily oral cyclophosphamide or intermittent intravenous cyclophosphamide. With early and aggressive therapy 75% to 80% of patients with PAN and 95% with WG respond initially to therapy. Relapses can occur, especially with rapid tapering of immunosuppression. The role of plasmapheresis is controversial and is usually reserved for patients requiring dialysis, those with lung haemorrhage or those who fail to respond to cyclophosphamide and steroids (65,110).
- d. Post infectious RPGN has a significantly better prognosis than most other forms of RPGN (111). No controlled trials of therapy have been reported and the role of immunosuppression has not yet been clearly defined.
- e. SLE : Crescentic nephritis associated with SLE requires aggressive therapy. High dose oral prednisone and later high dose "pulse" intravenous steroids are the mainstay of

therapy (112,113). Later studies appear to show reduced risk of end stage renal failure with the combination of steroids and cytotoxic drugs (114,115). Consensus about the superiority of pulse cyclophosphamide compared to oral cyclophosphamide has not been reached.

1.9 PROGNOSIS

The prognosis of RPGN is poor with an overall mortality in excess of 35%. Approximately 34% of patients have significant renal impairment after 2 years (6,116). Although aetiology influences prognosis, mortality between various groups is not significantly different. Idiopathic RPGN and anti-GBM disease result in end stage chronic renal failure more frequently than other forms of RPGN. Post infectious GN prognosis, although thought to be better, is probably similar to other forms of RPGN (47,49,117).

The most significant clinical prognosticator of poor outcome is oliguria at the time of presentation (51,117) and this is associated with twice the mortality. Mortality is bimodal and peaks in the 20 to 30 year age group. It rises again in patients over 50 years of age and equals the 20 to 30 year group in patients over 70 years. Meta analysis shows that creatinine levels at presentation in patients with RPGN do not correlate with the final degree of renal impairment (116).

The percentage of crescents on a renal biopsy may predict the prognosis. Patients with crescents in excess of 80% have twice the mortality of patients with 50% to 80% crescents (116). Diffuse

cellular proliferation, especially with neutrophil predominance, is associated with improved prognosis and indicates a recent onset of acute disease. Patients with MCGN are the exception to this general rule (51).

Renal function at the time of biopsy does not correlate well with histology. In patients where renal function improves there is a correlation between final glomerular filtration rate and the degree of tubular and interstitial damage at the time of original renal biopsy (51).

Immunosuppressive therapy has resulted in a significant decrease in both mortality and the severity of renal failure. Pulsed intravenous steroids with or without other immunosuppression and/ or plasmapheresis is superior to conventional oral immunosuppressive therapy with or without anticoagulants or antithrombotic therapy.

2.0 METHODS

The case records and renal biopsies of all patients with a diagnosis of RPGN at Groote Schuur Hospital between January 1977 and April 1991 were reviewed. Seventy three patients with over 50% of crescents on their biopsy specimens were selected for further study. Only biopsy samples with six or more glomeruli were considered adequate for study.

2.1 CLINICAL FEATURES

The demographic features studied were age, sex, race and social status.

The following presenting clinical features were reviewed:

- a) **Oliguria/anuria** (subjective assessment by attending physician).
- b) **Haematuria** (macroscopic at time of presentation).
- c) **Lethargy**.
- d) **Upper respiratory tract symptoms**.
- e) **Joint pains**.
- f) **Haemoptysis**.
- g) **Skin rash**.
- h) **Hypertension** was defined as either systolic blood pressure greater than 140 mm Hg and/or a diastolic blood pressure greater than 95 mm Hg. The blood pressure reading used was that recorded by the admitting registrar on presentation.
- i) **Oedema**.

2.2 SPECIAL INVESTIGATIONS

The following routine studies were done on all patients prior to renal biopsy:

- a) Urine examination with dipsticks, microscopy and 24 hour urine protein estimations (biuret method).
- b) Renal function measured as endogenous creatinine clearance and/or serum creatinine levels.
- c) Haematologic profile consisting of a full blood count, differential white cell count and erythrocyte sedimentation rate (ESR).
- d) Routine biochemistry performed on a sequential multiple analyzer computer (SMAC).
- e) Serology - Total complement, C3 and C4 levels, circulating immune complexes determined by a C1q assay, C-reactive protein concentrations, anti nuclear factor, anti-DNA antibody, anti-DNase B and anti-streptolysin O titers were measured. Routine testing for ANCA using an indirect immunofluorescent technique was introduced in 1988.
- f) Chest radiograph.

2.3 HISTOLOGY

The histology of the patients selected was reviewed with Dr M. Duffield. The haematoxylin and eosin and methenamine silver stained slides were retrieved from the archives of the Department of Pathology and the light microscopy was reviewed without knowledge of clinical details. The underlying type of glomerulonephritis was assessed where possible. Crescents were counted and classified as cellular or fibrous.

Sclerosed glomeruli, although possibly associated with crescents, were not counted as such. The percentage of crescents was estimated by dividing the sum of the fibrous and cellular crescents by the total number of glomeruli. The interstitium and tubules were examined for evidence of interstitial infiltrate, chronic fibrosis and signs of acute tubular necrosis. The presence of hypertensive changes or vasculitis as well as its severity was assessed. Changes were graded as mild, moderate or severe.

The definition of acute tubular necrosis for purposes of this study was as follows. Mild: Flattening of epithelium with variability of nuclear staining and marked tubular vacuolation adjacent to normal tubules. Moderate: Mitotic activity with tubular sloughing without complete blockage of tubular lumina. Severe: Mitotic activity, syncytia formation and extensive tubular sloughing causing complete blockage of tubular lumens. An overall assessment of the clinical severity of renal disease was attempted on the basis of the light microscopy.

Immunofluorescent microscopy was performed using fluoresceine labelled rabbit anti-human IgG, IgM, IgA, C3 and fibrinogen antibody. Specimens for electron microscopy were fixed in 5% glutaraldehyde, resin embedded, sectioned and stained with osmium, and were viewed on a Hitachi transmission electron microscope.

2.4 TREATMENT AND FOLLOW UP

Treatment and outcome were reviewed from patient records.

Supportive therapy including acute dialysis, blood pressure control and fluid management was instituted. Specific therapy included "pulse" medrol (500 or 1000 mg of methylprednisolone administered intravenously for 3 consecutive days), oral prednisone, cyclophosphamide (either administered intravenously or orally for a variable length of time depending on the condition treated) and plasmapheresis (anti-GBM group only). Length of follow up was recorded. The cause of death was assessed where possible in those that died.

2.5 STATISTICAL ANALYSIS

Patient data was captured on a personal computer using D BASE III. Frequencies and outcomes were examined and compared in a four-fold tabular analysis. Odds ratios (OR), 95% confidence limits (CI) and p-values based on chi-squared or Fishers exact tests were calculated. Continuous variables were compared using students t-test. P values of <0,05 were considered significant.

3.0 RESULTS

Records of 1 898 renal biopsies performed at Groote Schuur Hospital from 1977 to April 1991 containing at least six glomeruli were reviewed. Seventy three (3.8%) had more than 50% crescents. The distribution of clinical diagnosis is illustrated in figure 1. The total study group (RPGN) is divided into post infectious RPGN (PIGN), RPGN associated with systemic lupus erythematosus (SLE), idiopathic RPGN (IDIO), RPGN associated with vasculitis (VASC) and a miscellaneous group.

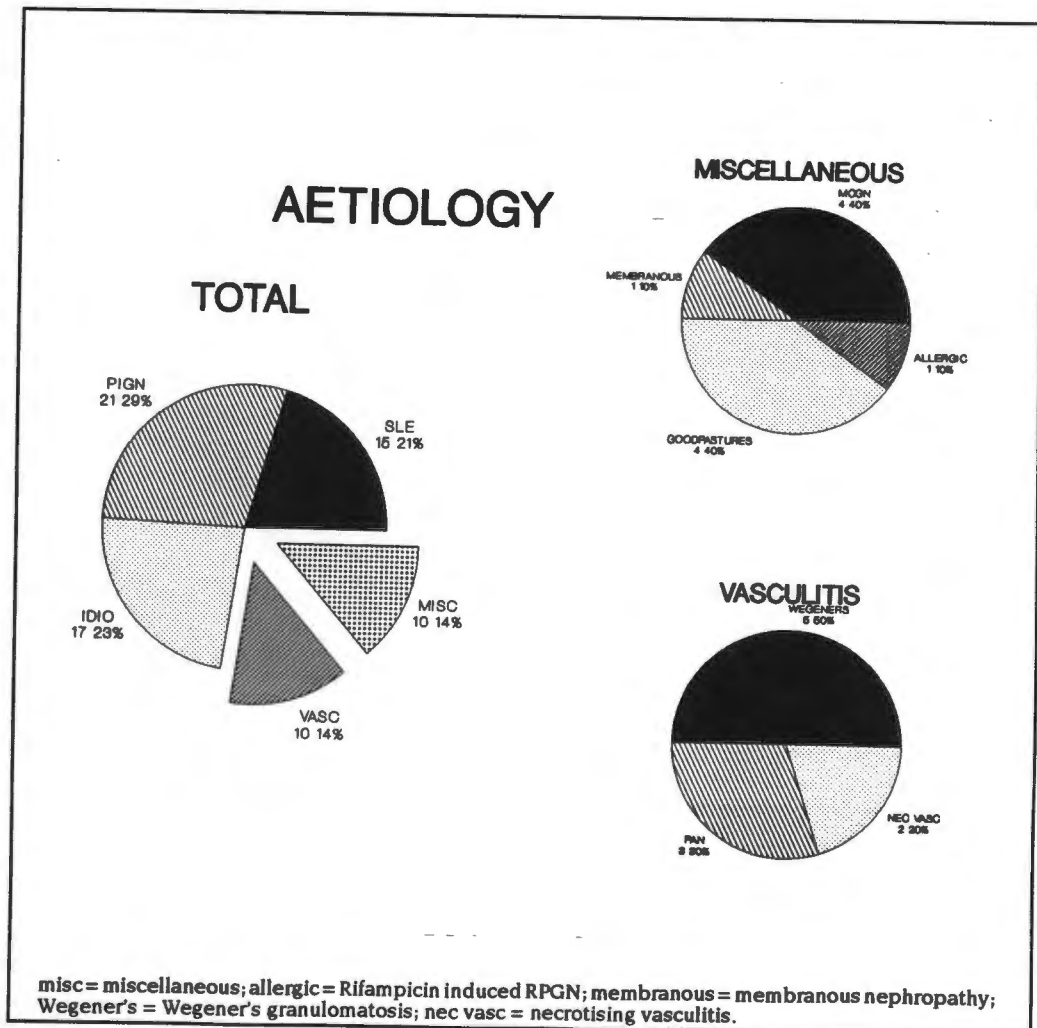


Figure 1: Aetiology of RPGN

3.1 MISCELLANEOUS GROUP

The miscellaneous group comprising 10 patients is discussed separately because the small numbers precluded statistical analysis.

3.1.1 Goodpasture's Syndrome

Four patients had Goodpastures syndrome. Three patients had a positive diagnosis by the finding of linear fluorescence on renal biopsy and one had a positive test for anti-GBM antibody. Two patients were white, one black and one of mixed racial origin. Their ages were 14, 23, 32 and 63 years. There were three females and one male. Two patients came from poor and two from good social circumstances.

All four patients presented with haemoptysis, three had dyspnoea and three upper respiratory tract symptoms. Two patients presented with oliguria and one with macroscopic haematuria. None of the patients had either rash or arthralgia. Three patients demonstrated evidence of systolic hypertension (above 140 mm Hg) and two patients diastolic hypertension (above 95 mm Hg). All four patients had clinical evidence of oedema.

Urinalysis demonstrated microscopic haematuria and proteinuria in three patients. Two patients had either granular or cellular casts and one patient was anuric. One patient had creatinine clearances less than 10 ml/min, one a clearance of 34 ml/min and one a clearance of 84 ml/min. Three patients had elevated serum

creatinine levels. The anuric patient had a serum creatinine level of 2103 $\mu\text{mol/l}$. Two patients had serum creatinine levels of approximately 350 $\mu\text{mol/l}$ and the patient with the clearance of 84 ml/min a serum creatinine level of 116 $\mu\text{mol/l}$. Urinary protein of less than 1.5 gm/day was found in two of the patients. One patient had nephrotic range proteinuria of 4.6 gm/day.

All patients had normochromic, normocytic anemia with haemoglobins ranging from 5.2 to 10.9 gm.%. The platelet counts were normal and the ESR raised in all subjects. Three patients had ESR levels greater than 100 mm in the first hour and the other an ESR of 50 mm in the first hour. Two patients had low total complement levels (normal range 160 to 320). All three patients tested had low C3 levels with a range of 80-100 units (normal 115 to 230). C4 levels were low in two of three patients tested and ranged from 16 to 35 units (normal 20 to 50). Circulating immune complex levels were normal in three of the four patients tested. C reactive protein was raised in one of two patients tested. All four patients demonstrated an interstitial infiltrate on chest radiograph at presentation.

All patients had a crescentic nephritis with crescents ranging from 54% to 86%. Three patients had less than 80% crescents. The anuric patient had 17 of 37 glomeruli sclerosed with 100% of the remaining glomeruli having crescents. This patient had a moderate chronic infiltrate and no evidence of acute tubular necrosis on histology. The immunofluorescence showed classical linear Ig G staining.

Interstitial infiltrate was mild in one patient and moderate in the other three. One patient had evidence of acute tubular necrosis. Two patients demonstrated evidence of mild chronic interstitial or tubular damage and one patient had evidence of moderate hypertensive changes. Three patients demonstrated the classical linear IgG staining and one patient had no staining on immunofluorescence but had a positive anti-GBM antibody.

All patients were treated with intravenous "pulse" medrol followed by prednisone and cyclophosphamide. Two patients had plasmapheresis. The patient presenting with a serum creatinine of 2103 $\mu\text{mol/l}$ and all glomeruli either sclerosed or crescents did not recover renal function despite treatment with plasmapheresis. Another patient developed end stage renal failure within 6 months of presentation and is currently on dialysis. The two patients who recovered received plasmapheresis. They presented in March 1979 and January 1991 and had a creatinine levels of 104 and 124 $\mu\text{mol/l}$ respectively at the end of their follow-up periods.

3.1.2 Mesangiocapillary glomerulonephritis

All four patients in this subgroup were males aged 27, 32, 56 and 66 years. Three patients were of mixed origin and one was black. All came from poor socio-economic circumstances.

Two presented with macroscopic haematuria, two with symptoms of lethargy, one with oliguria and one with arthralgia. All patients presented with systolic hypertension and three with diastolic

hypertension. All had peripheral oedema and haematuria and proteinuria on urinalysis.

Urine microscopy revealed casts in three patients. Nephrotic range proteinuria with 3.7, 7.3, 8.5 and 23.7 gm./day was present. Two patients were anaemic. One had a haemoglobin of 8.7 gm.% and a mean cell volume of 75, while the other had a haemoglobin of 10 gm.% and a mean cell volume of 84. Platelet counts were normal in all subjects. ESR was elevated at 30, 36, 63 and 92 mm respectively in the first hour. Renal function was abnormal in all subjects. Serum creatinine levels were 140, 200, 363 and 396 umol/ liter and the corresponding creatinine clearances were 32, 28, 24 and 8 ml/minute. Two patients had total complement levels of less than 70 units. A single patient had a C3 and a C4 level performed, both of which were low. Circulating immune complex levels performed on three patients were elevated at 7.6, 24, and 69% binding. C reactive proteins performed on two patients were 1.7 and 3.1 mg.%. Two chest radiographs were normal, one demonstrated an interstitial pattern and the other an alveolar pattern.

The percentage crescents in the patients were 53%, 67%, 69% and 76%. There was no evidence of vasculitis. One patient had mild, two moderate and one severe interstitial infiltrate. Three patients had mild evidence of ATN, one mild chronic interstitial changes and one moderate evidence of hypertension.

Two patients were treated with intravenous "pulse" medrol followed by oral prednisone and cyclophosphamide. One patient

with a presenting serum creatinine of 1329 $\mu\text{mol/l}$ improved and had a serum creatinine of 322 $\mu\text{mol/l}$ in July 1991, two years after initial diagnosis. A single patient died within a month of diagnosis. One patient, treated with methylprednisolone 500 mg intravenously daily for three days and prednisone 60 mg per day and cyclophosphamide 100 mg per day orally, progressed to end stage renal failure 15 months after diagnosis and is currently on dialysis. One patient was lost to follow up.

3.1.3 Membranous glomerulonephritis

The patient was a 33 year old male of mixed origin and came from good social circumstances. He had a background of membranous nephropathy previously diagnosed on biopsy two years prior to this presentation. His presenting features on this occasion were lethargy, slight oedema and a blood pressure of 150/90 mm Hg. He was passing normal volumes of urine. Urinalysis revealed microscopic haematuria, proteinuria and urinary casts. Twenty four hour urinary protein excretion was 6.8 gm. The patient had a haemoglobin of 8.2 gm.% and an ESR of 150 mm in the first hour. Presenting creatinine clearance was 3 ml/min with a urine volume of 700 ml and serum creatinine of 1245 $\mu\text{mol/l}$. Complement and CIC levels were normal. C reactive protein was 0.1 mg%. Chest radiograph was normal. Histology revealed 100% crescents of which 50% were fibrous and 50% cellular. Interstitial infiltrate was moderately severe. No electron microscopy or immunofluorescence was performed. Treatment was "pulse" medrol, prednisone and cyclophosphamide. The patient did not recover renal function and required chronic dialysis.

3.1.4 Rifampicin associated RPGN

The patient was a 26 year old black male of poor social circumstances who had recently been diagnosed as having pulmonary tuberculosis. His treatment with rifampicin, isoniazid, pyrazinamide and ethambutol commenced about three weeks prior to presentation. He presented with lethargy, pedal oedema and a blood pressure of 140/80 mm Hg. Urinalysis revealed haematuria, proteinuria and casts. Twenty four hour urinary protein excretion was 12 gm. Haemoglobin was 9.7 gm % and ESR 71 in the first hour. Presenting creatinine clearance was 11.8 ml/min and serum creatinine 635 umol/l. Complement and CIC levels were normal. C reactive protein was 8.8 mg%. Chest radiograph was compatible with tuberculosis. Histology revealed 73% crescents of which 56% were fibrous and 44% cellular. Interstitial infiltrate was severe. No electron microscopy or immunofluorescence was performed. The patients anti-tuberculous therapy was stopped and he was treated with "pulse" medrol, prednisone and cyclophosphamide. When his renal function had recovered anti-tuberculous therapy without rifampicin was recommenced. He was discharged from the clinic 14 months after admission with a serum creatinine of 75 umol/l.

3.2 OTHER GROUPS

3.2.1 Demographic Features

Age: The distribution of ages is demonstrated in figure 2.

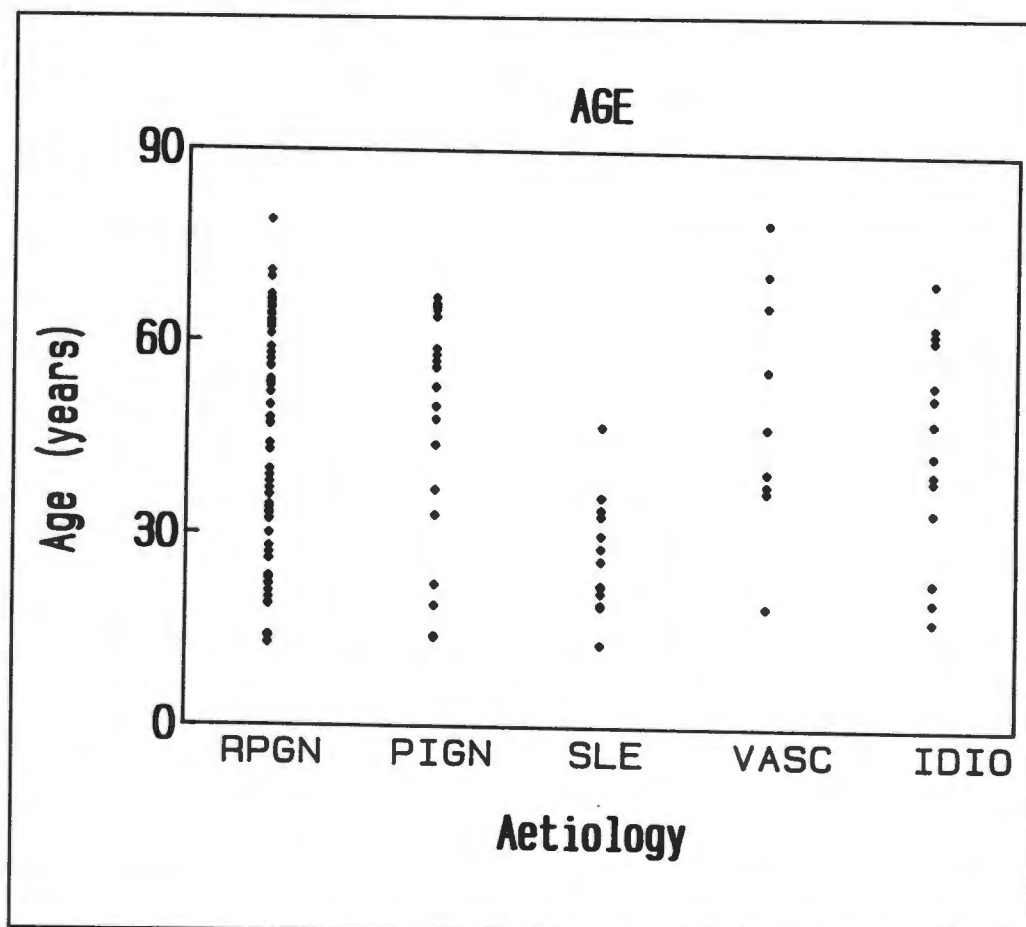


Figure 2: Age distribution in the total group and according to aetiology of RPGN

The mean age for the population studied was 41 years with a wide range (13-79 years). The PIGN group had an average age of 48 years (range 14-66 years), the SLE group average age was 28 years (range 13-47 years), the vasculitis group average age was 50 years (range 19-79 years) and the idiopathic group average age was 44 (range 17-70 years).

Race: The race distribution is shown in figure 3.

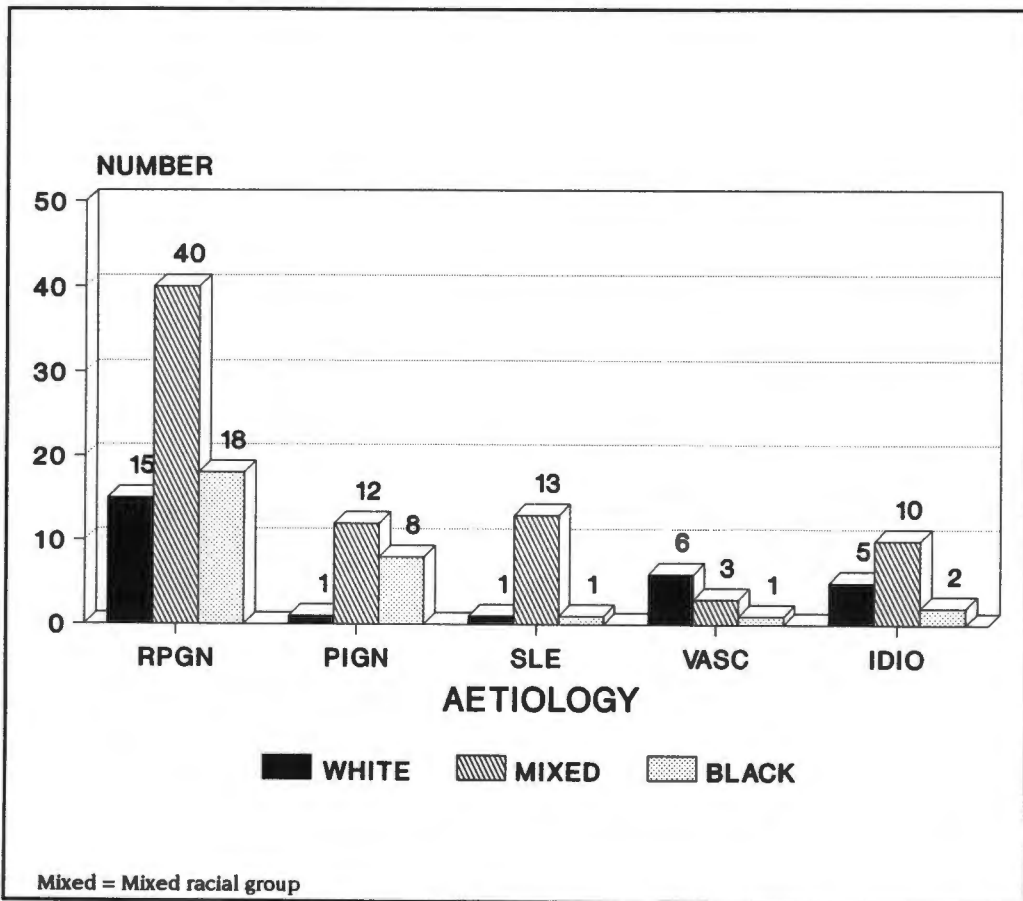


Figure 3: Racial distribution in the total group and according to aetiology of RPGN

Sex: Sex distribution is demonstrated in figure 4.

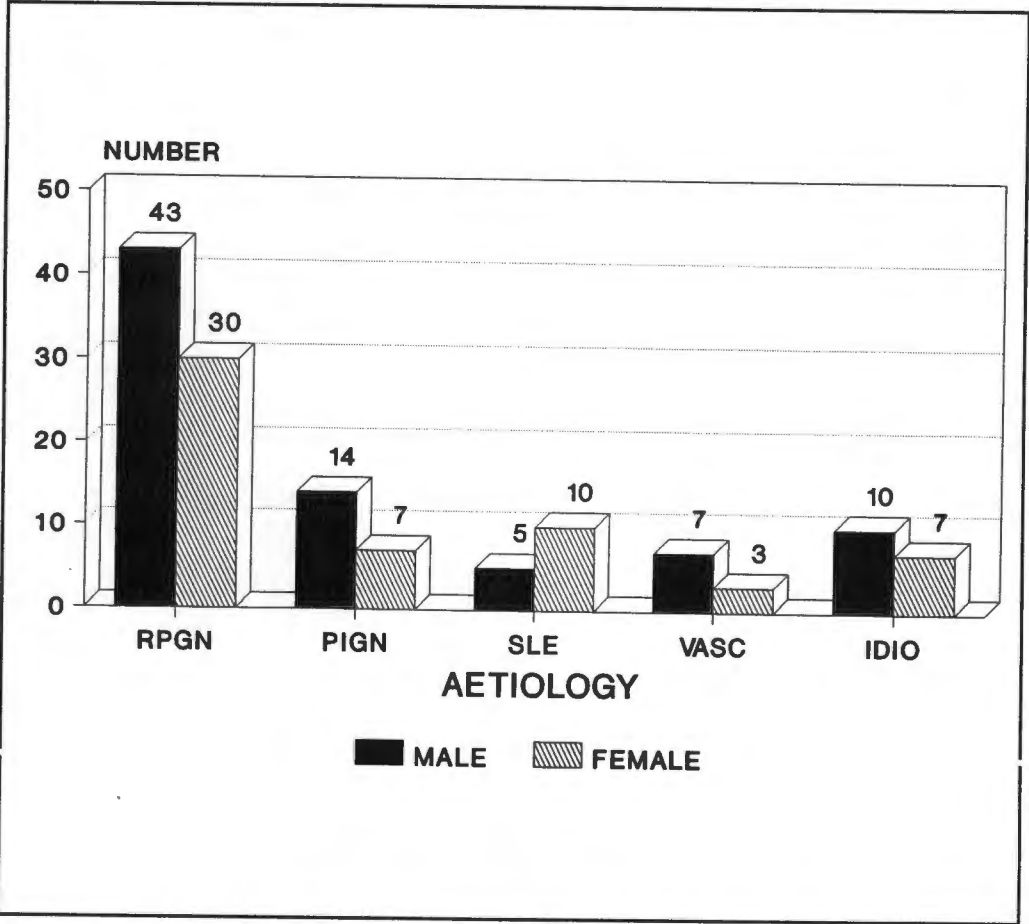


Figure 4: Sex distribution in the total group and according to aetiology of RPGN

Social status: A subjective assessment of the social status of patients as poor, intermediate and good was made on reviewing the records. This is based on employment status and living conditions. Results are shown in figure 5.

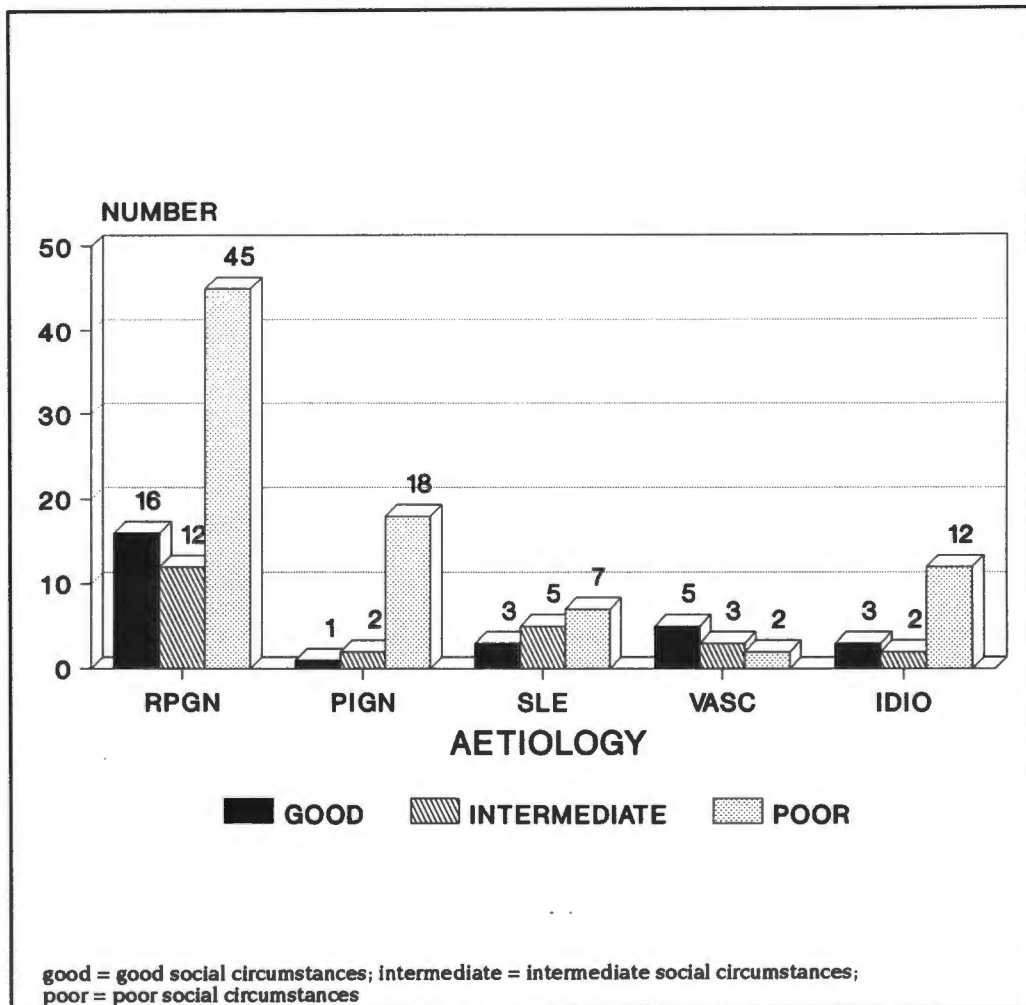


Figure 5: Social class in the total group and according to aetiology of RPGN

3.2.2 Clinical Presentation

The presenting clinical features in RPGN are shown in figure 6. The duration of symptoms prior to presentation could not be accurately determined from the data available. The following trends were observed. Haemoptysis was more common in the vasculitic

group, being present in four (40%) cases. None of the patients in the vasculitic group presented with oliguria and only one patient had macroscopic haematuria. Five (29%) of the idiopathic group complained of upper respiratory tract symptoms in contrast to eight (80%) in the vasculitis group. Arthralgia was an uncommon symptom in the PIGN and idiopathic groups with three (14%) and two (12%) respectively. Oedema was less common amongst the vasculitis group, affecting four patients (40%). Rash was an uncommon presenting symptom and did not occur in the PIGN group. Two (12%) of the idiopathic group, three (30%) of the vasculitis group and six (40%) of the SLE group presented with a rash.

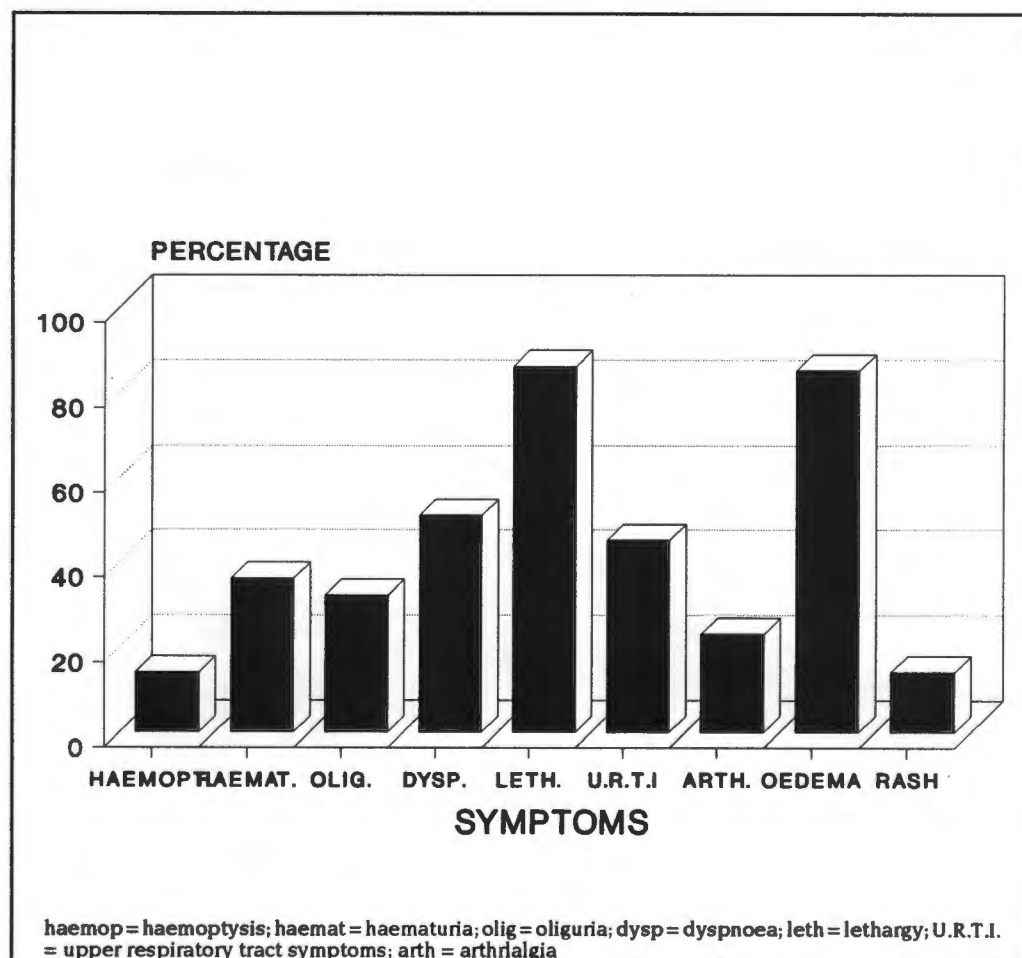


Figure 6: Clinical features in the RPGN group

The incidence of hypertension at presentation is shown in figure 7.

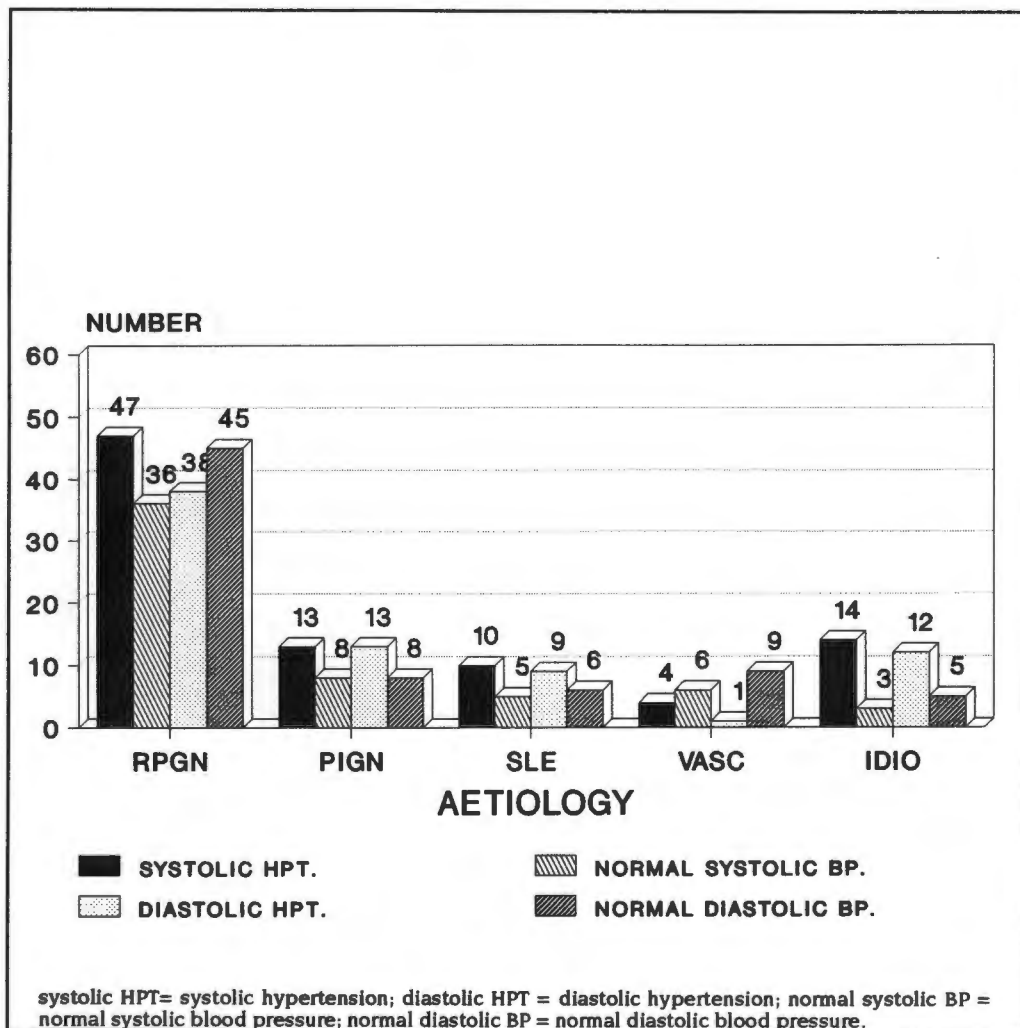
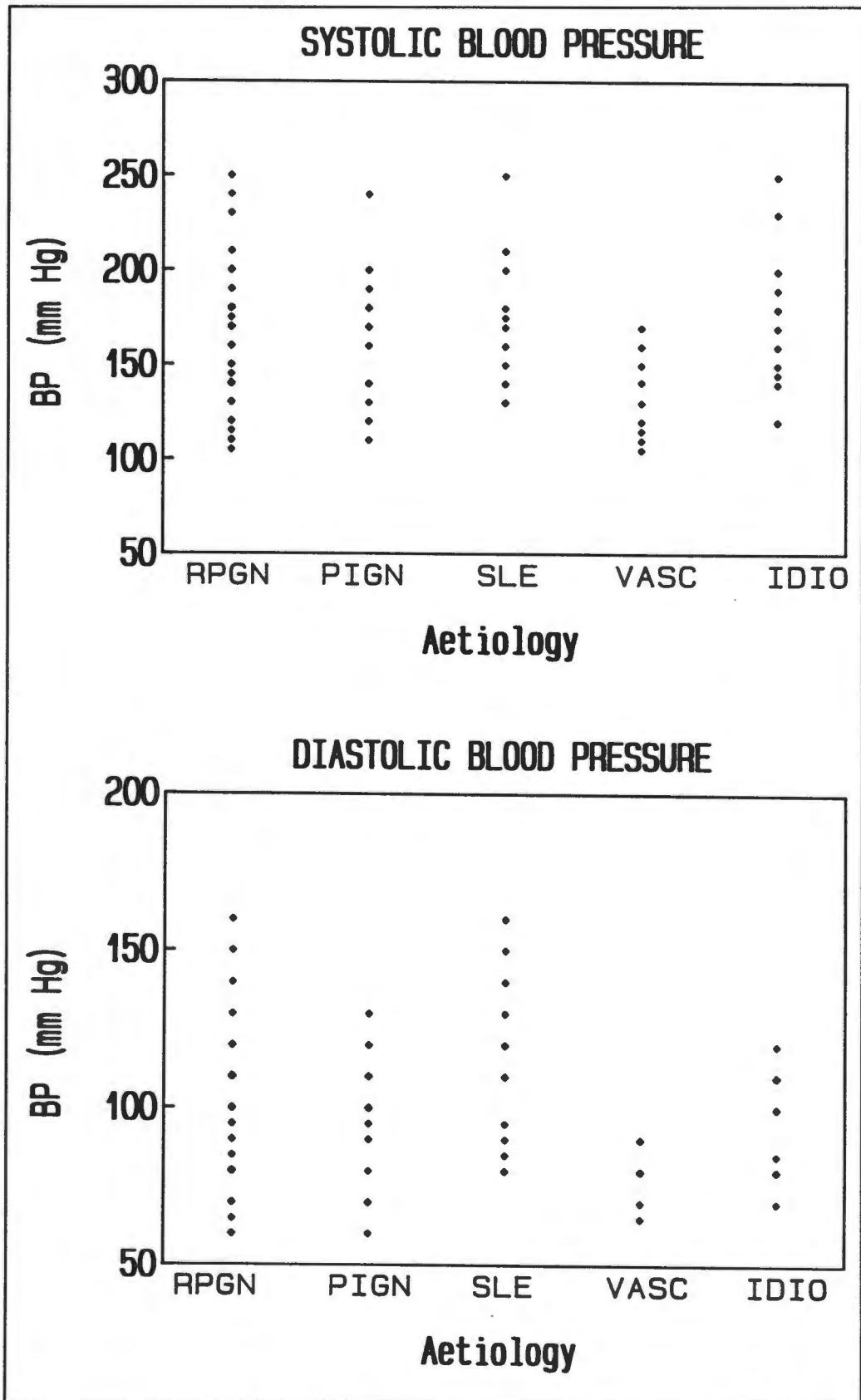


Figure 7: Incidence of hypertension in the total group and according to aetiology of RPGN

There was a wide range of blood pressures and their distributions are shown in figures 8 and 9.



Figures 8 and 9: Systolic and diastolic blood pressure distributions in the total group and according to aetiology of RPGN

Systolic and diastolic blood pressures were significantly lower in the group with vasculitis ($t=3.7$ $p<0.01$) and ($t=5.64$ $p<0.01$) at presentation respectively. Serial blood pressure measurements were not available for analysis.

3.2.3 Investigations

The urinary findings in the groups studied were similar, as shown in figure 10.

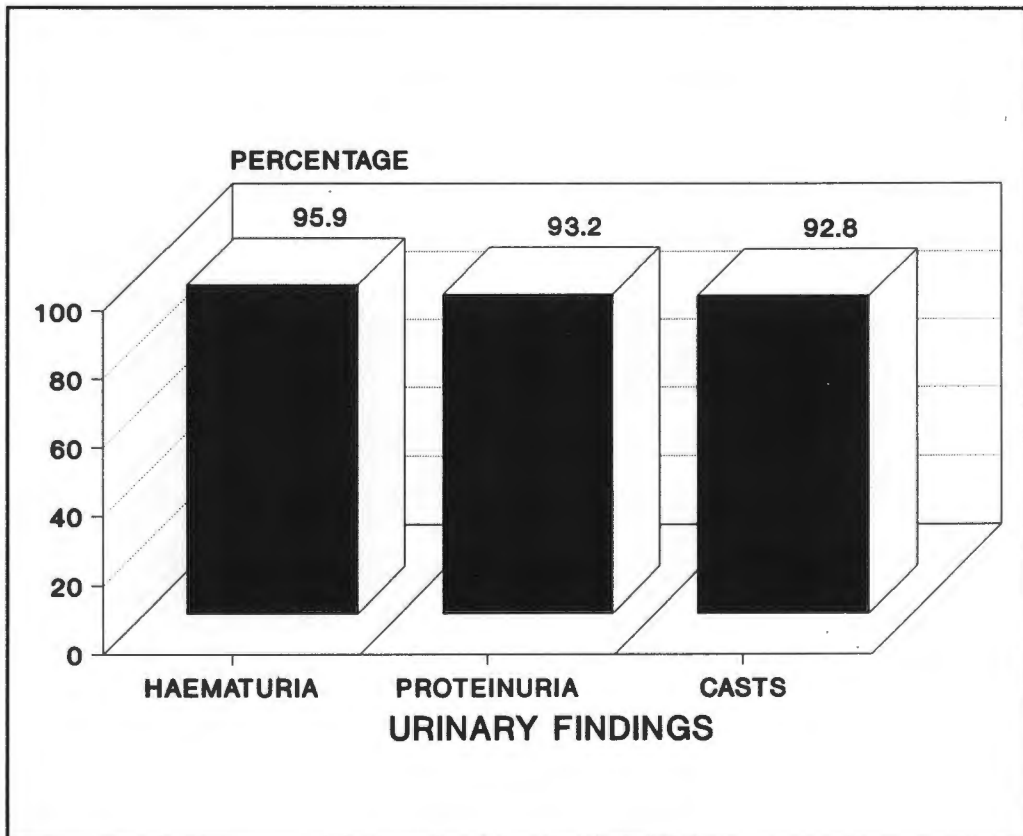
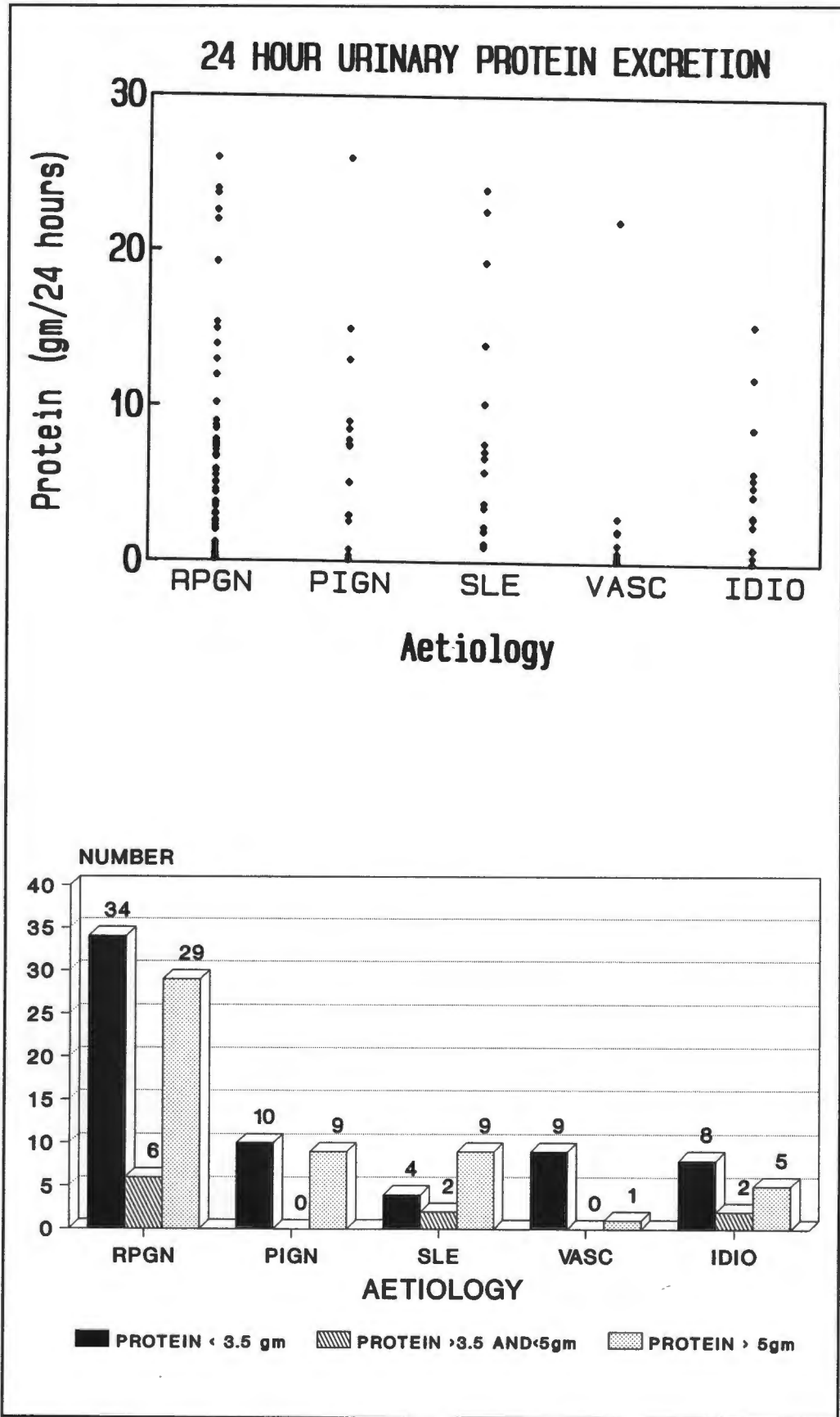


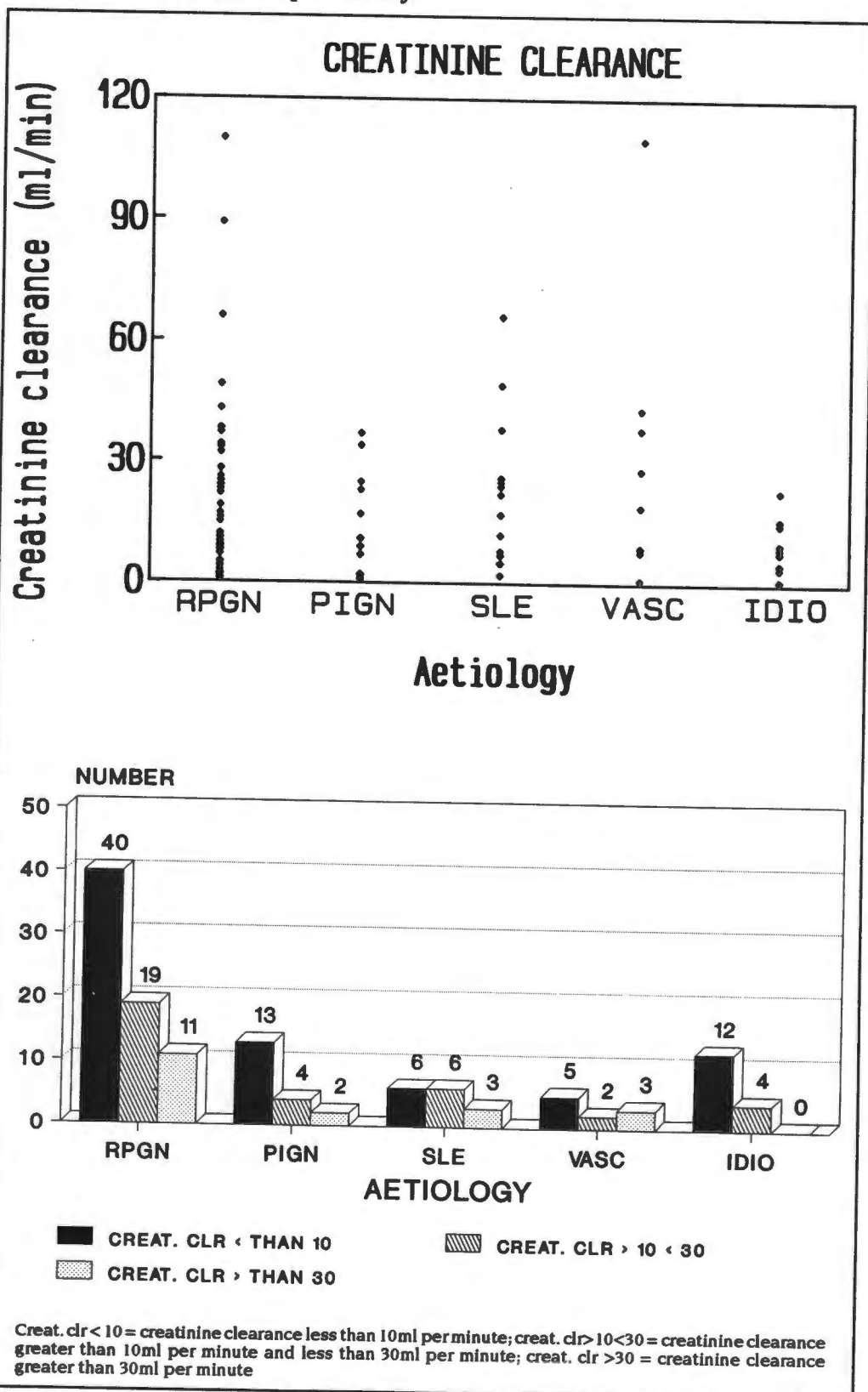
Figure 10: Urinary findings in the RPGN group

Figure 11 shows the distribution of patients' 24 hour urine protein levels and figure 12 the incidence of nephrotic syndrome.



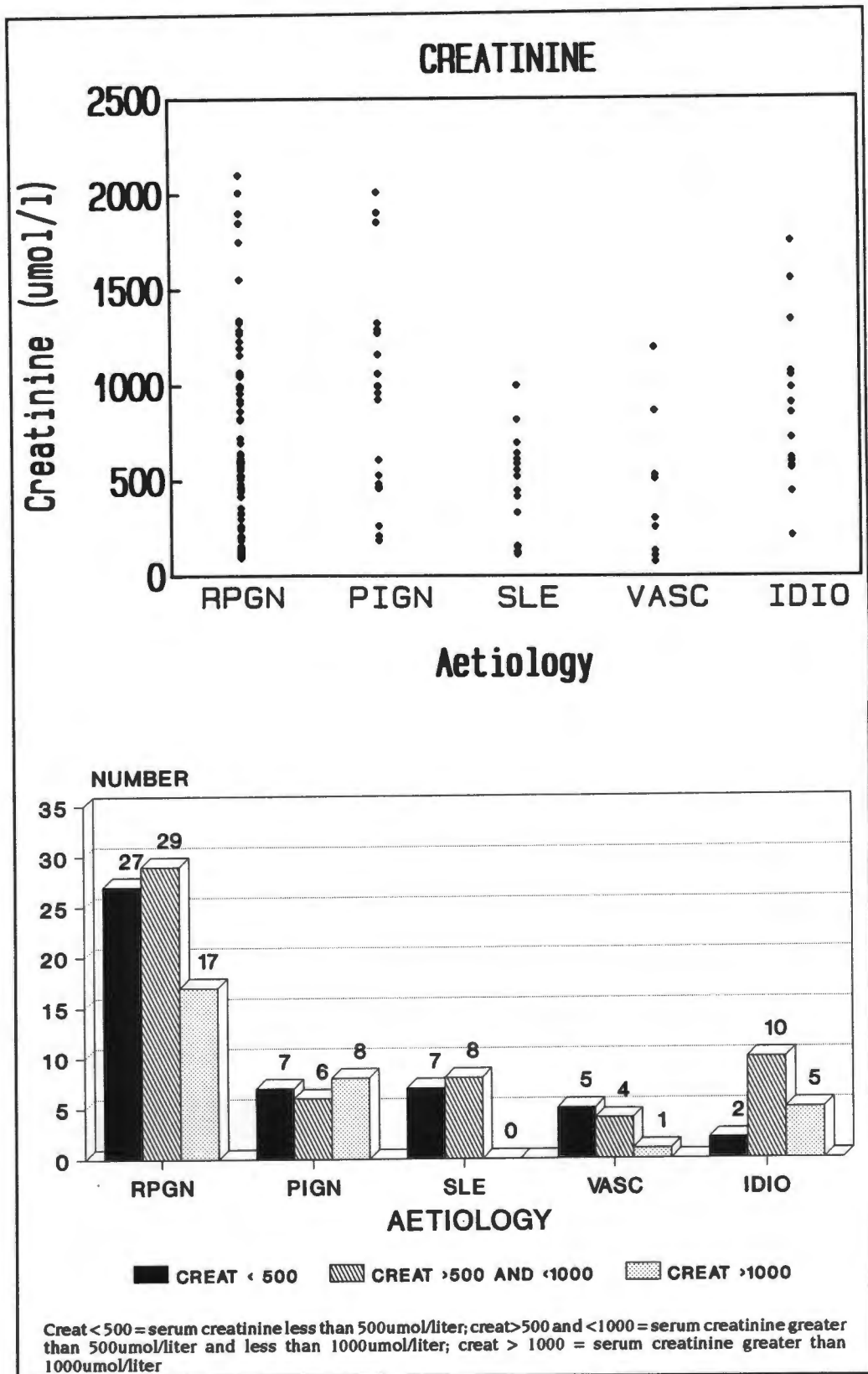
Figures 11 and 12: Distribution and incidence of 24-hour urinary protein in the total group and according to aetiology of RPGN

The distribution of endogenous creatinine clearance is shown in figures 13 and 14 respectively.



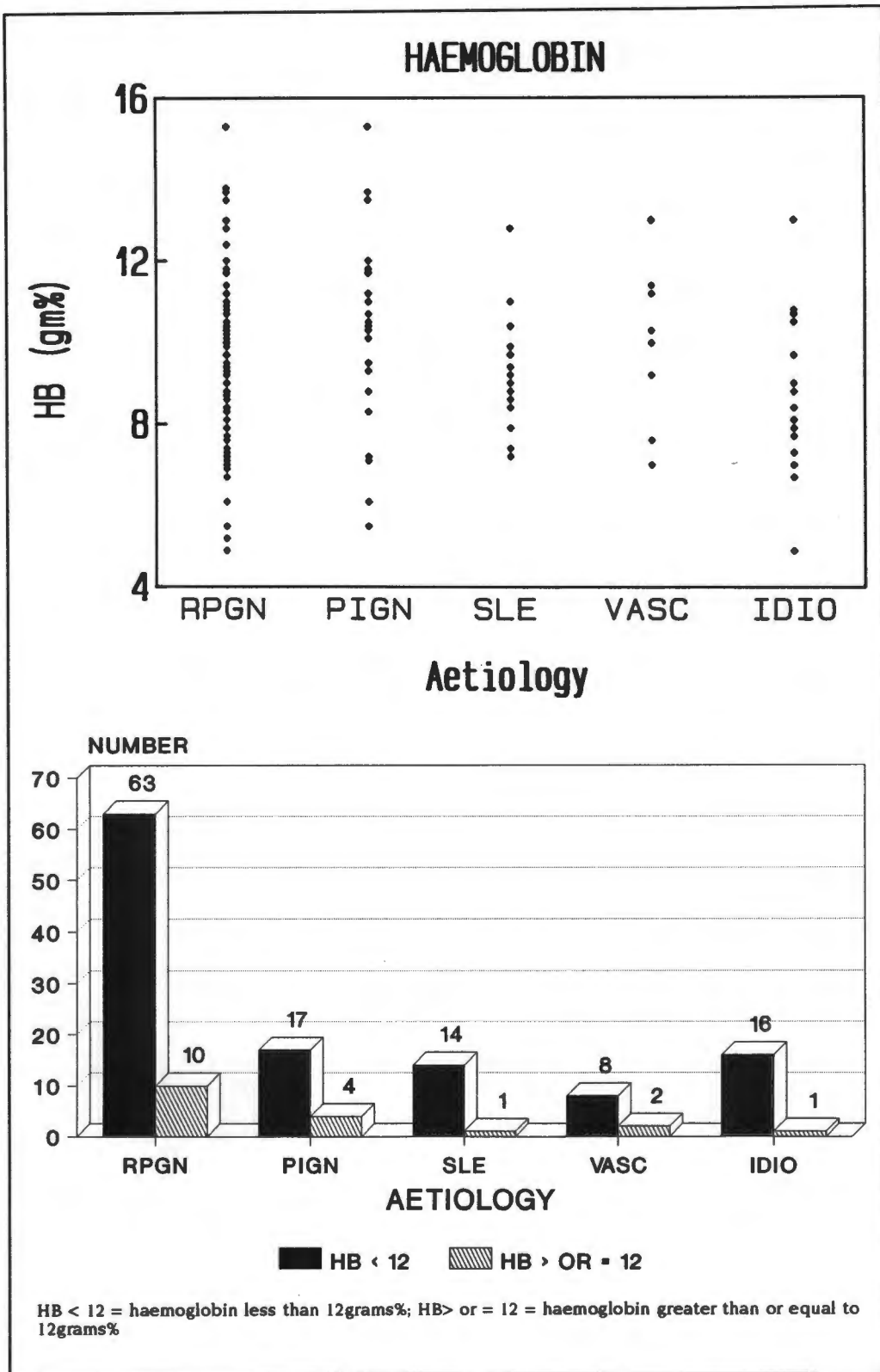
Figures 13 and 14: Distribution and incidence of creatinine clearance in the total group and according to aetiology of RPGN

The distribution of serum creatinine is shown in figures 15 and 16.



Figures 15 and 16: Distribution and incidence of serum creatinine in the total group and according to aetiology of RPGN

The distribution of haemoglobin levels is shown in figure 17 and the incidence of anaemia is shown in figure 18.



Figures 17 and 18: Distribution of haemoglobin and incidence of anaemia in the total group and according to aetiology of RPGN

Platelet counts were above the lower limit of normal in all the groups. However thrombocytosis was more common in the vasculitis group, as seen in figure 19.

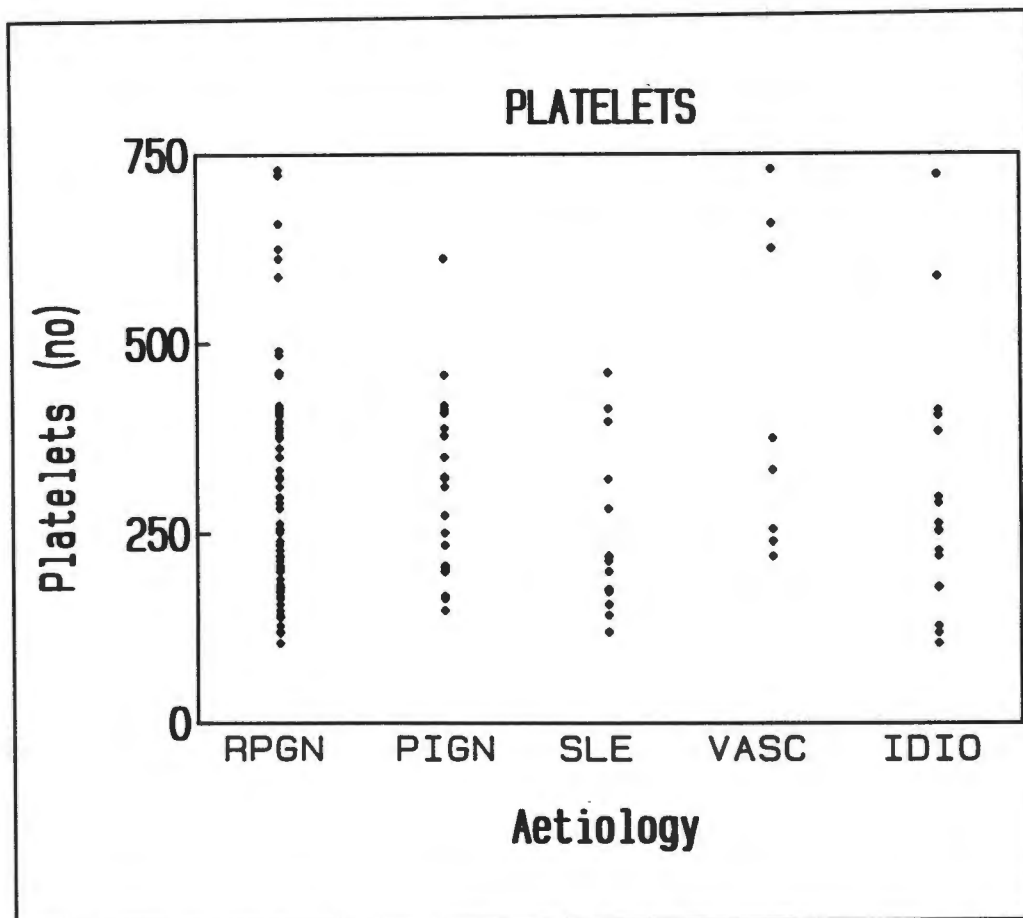
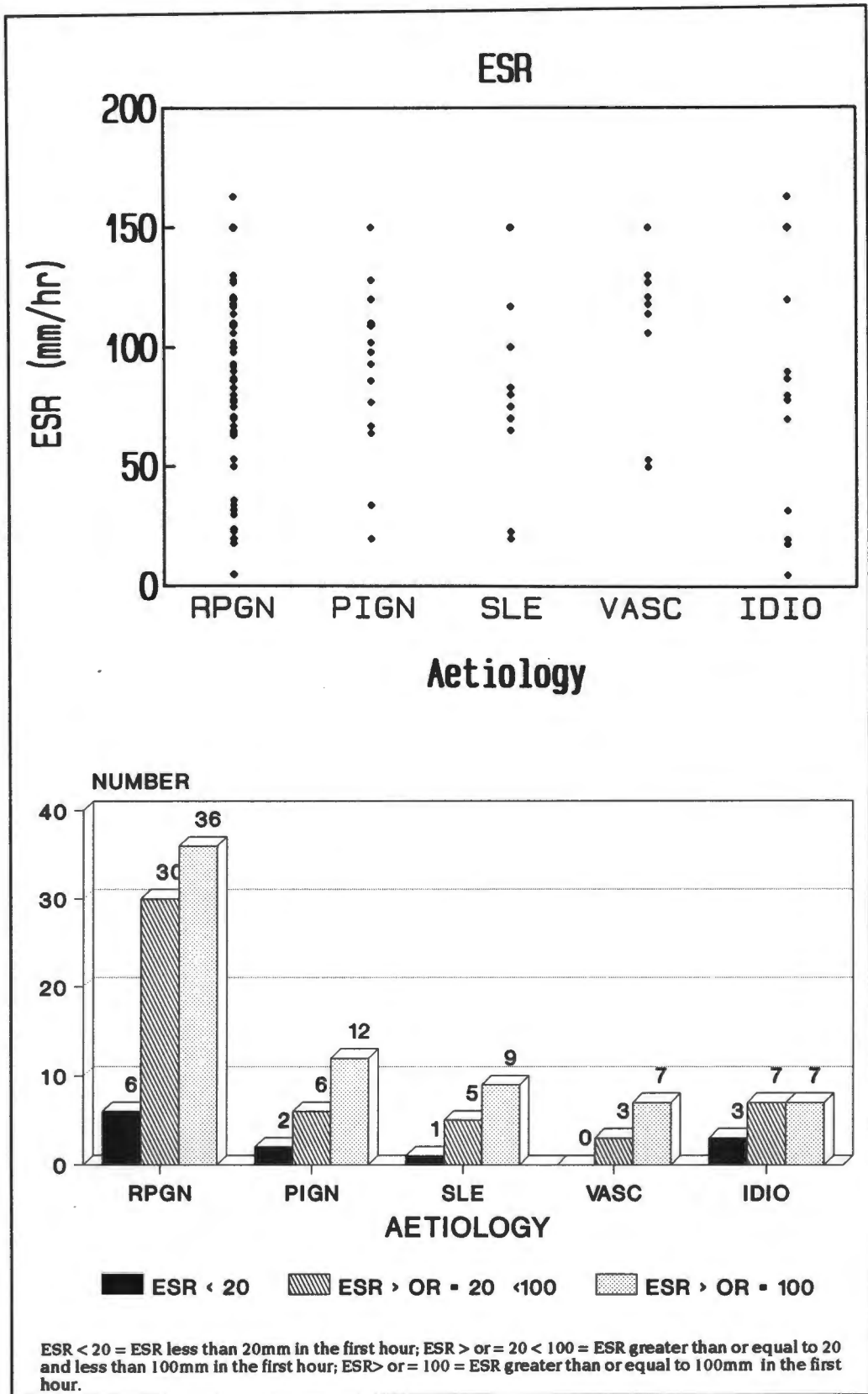


Figure 19: Distribution of platelets in the total group and according to aetiology of RPGN

The distribution of ESR rates is demonstrated in figure 20 and the incidence of ESR rates above 100 mm in the first hour in figure 21. Only six patients in the RPGN group had a normal ESR (below 20 mm in the first hour).



Figures 20 and 21: Distribution and incidence of ESR in the total group and according to aetiology of RPGN

Ten (66.6%) and 11 (73%) of 15 patients were positive for anti nuclear factor and anti DNA antibodies respectively in the SLE group. Nine (43%) and 13 (62%) of 21 patients in the PIGN group were positive for anti streptolysin O titers and anti DNase B titers.

ANCA assays were unavailable until 1988 and were therefore performed on only 11% of the RPGN group. Two tests were performed on patients in the vasculitis group of patients. A patient with WG had a significant titer of 1:40 while a patient with microscopic PAN had a borderline titer of 1:20. Six patients (three in the PIGN group, two in the idiopathic group and one with anti-GBM disease) had undetectable titers.

The distribution of total complement, C3 and C4 are shown in figures 22, 23 and 24. Their normal values are 160 to 300 units, 115 to 230 units and 20 to 50 units respectively.

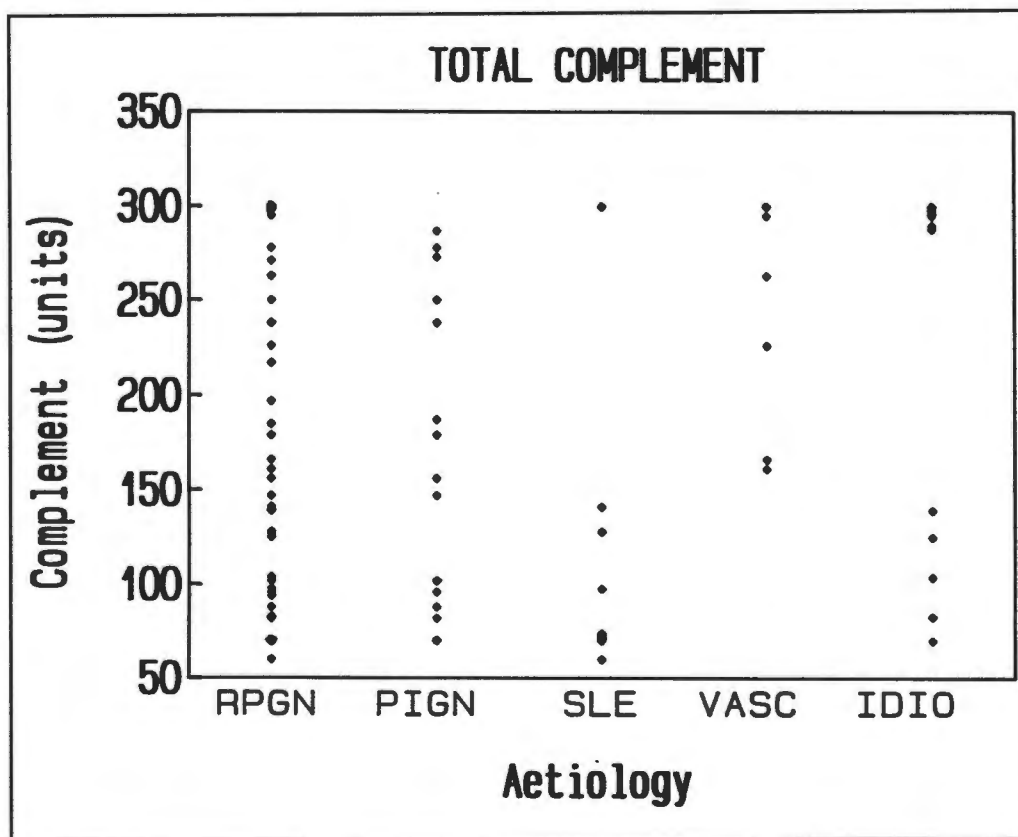
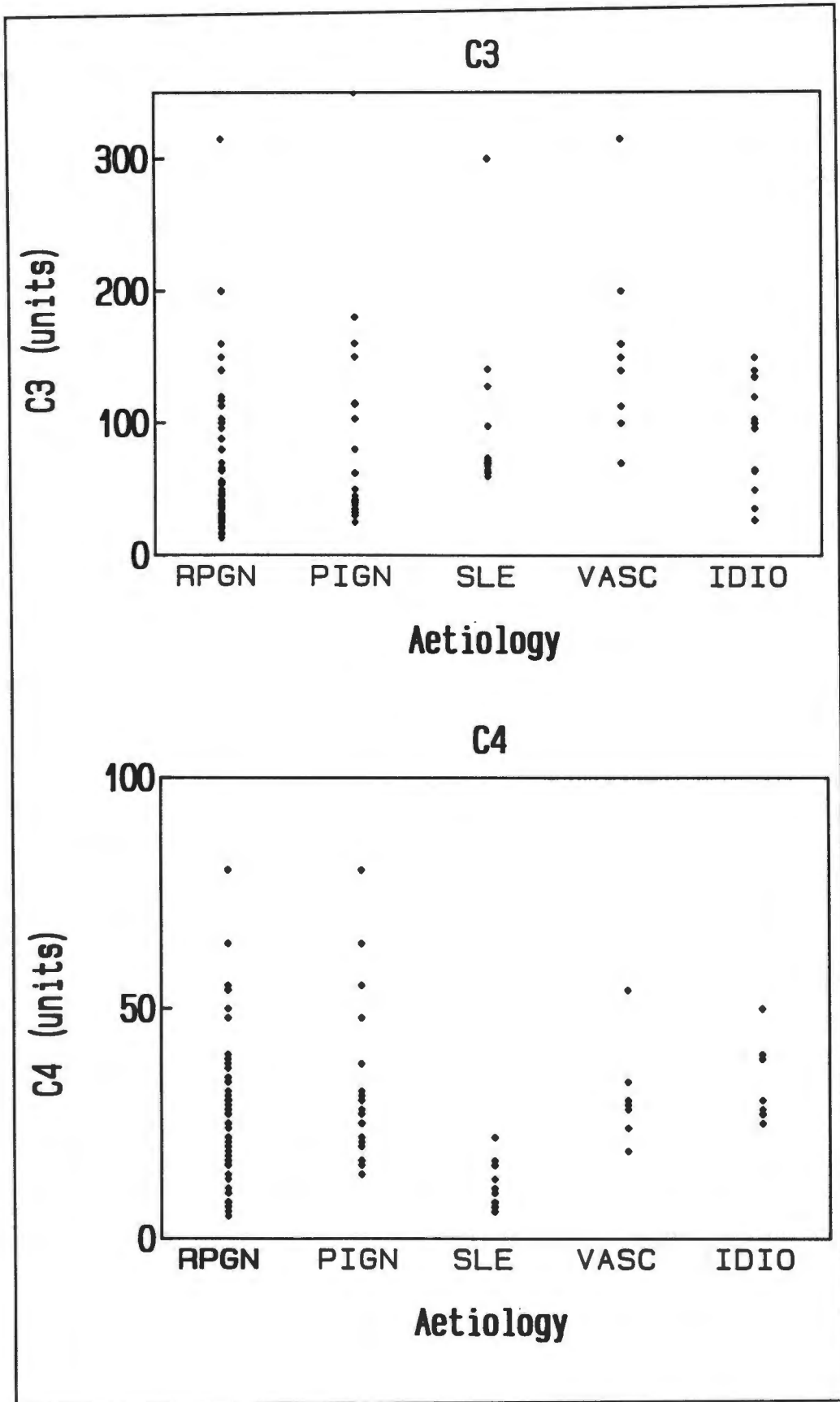


Figure 22: Distribution of total complement in the total group and according to aetiology of RPGN



Figures 23 and 24: Distribution of C3 and C4 in the total group and according to aetiology of RPGN

The incidence of hypocomplementemia is shown in figure 25.

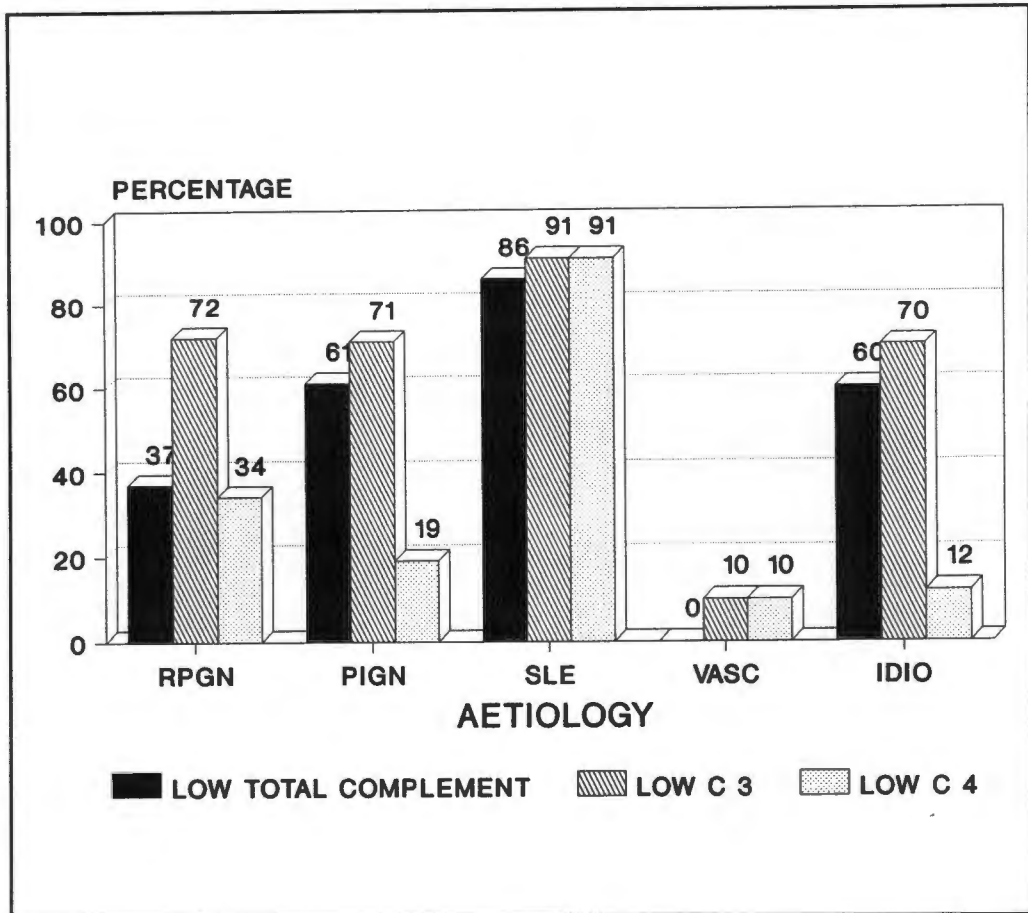
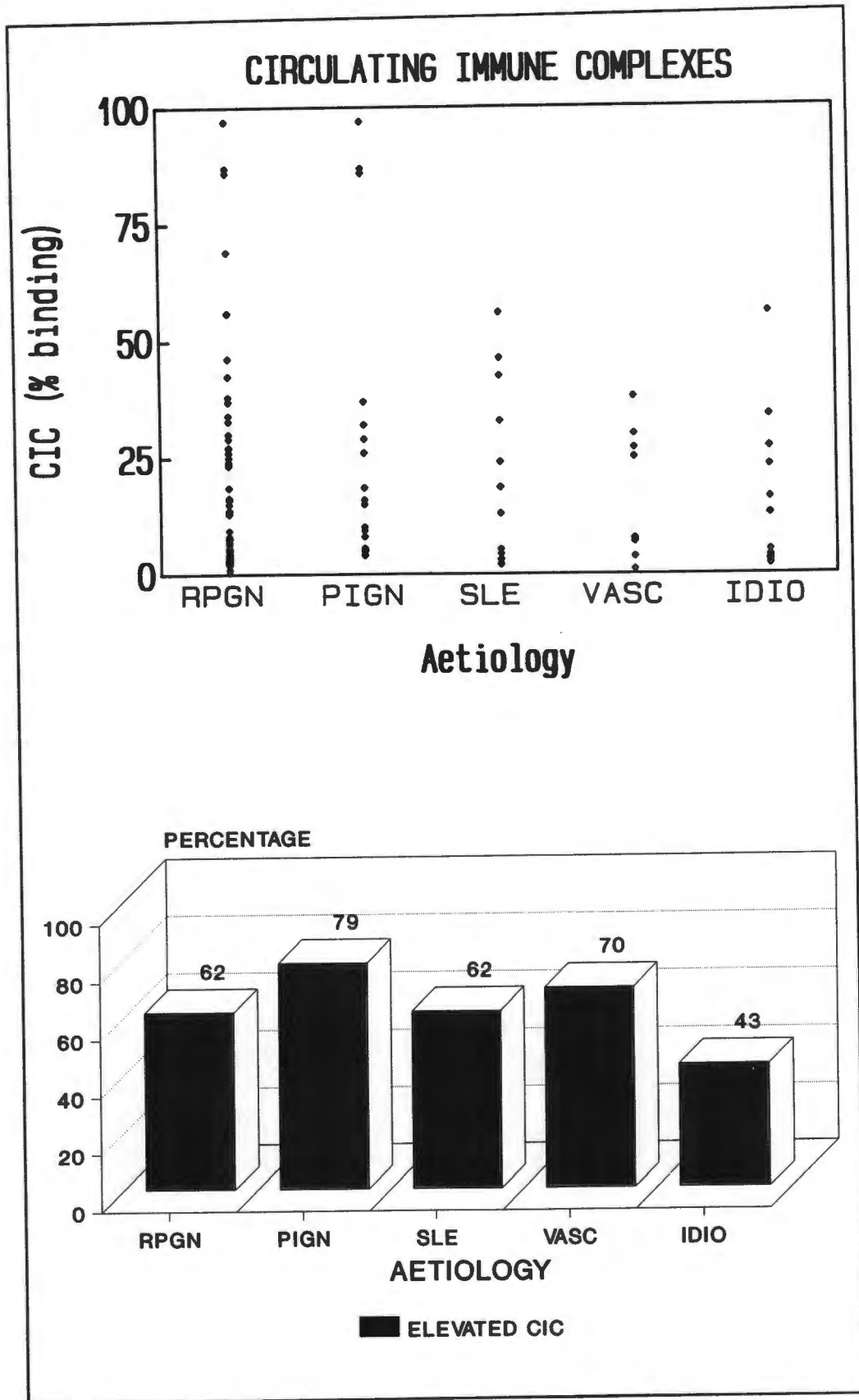


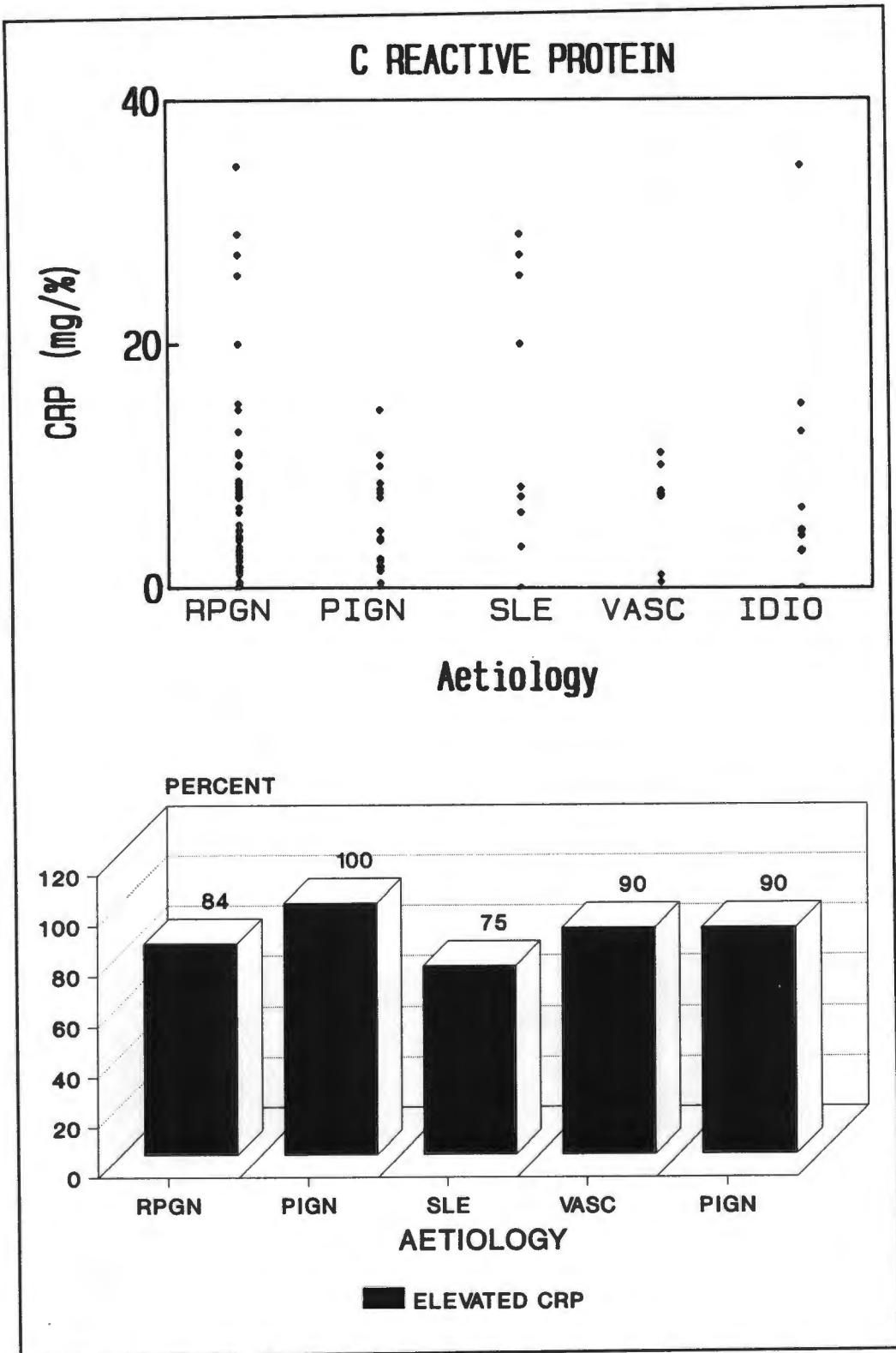
Figure 25: Incidence of hypocomplementemia in the total group and according to aetiology of RPGN

The distribution of CIC levels is shown in figure 26 and the incidence of high CIC levels in figure 27.



Figures 26 and 27: Distribution and incidence of circulating immune complexes in the total group and according to aetiology of RPGN

Figure 28 shows the distribution of CRP and figure 29 the incidence of elevated CRP levels.



Figures 28 and 29: Distribution and incidence of C reactive protein in the total group and according to aetiology of RPGN

Figure 30 demonstrates the chest radiograph findings.

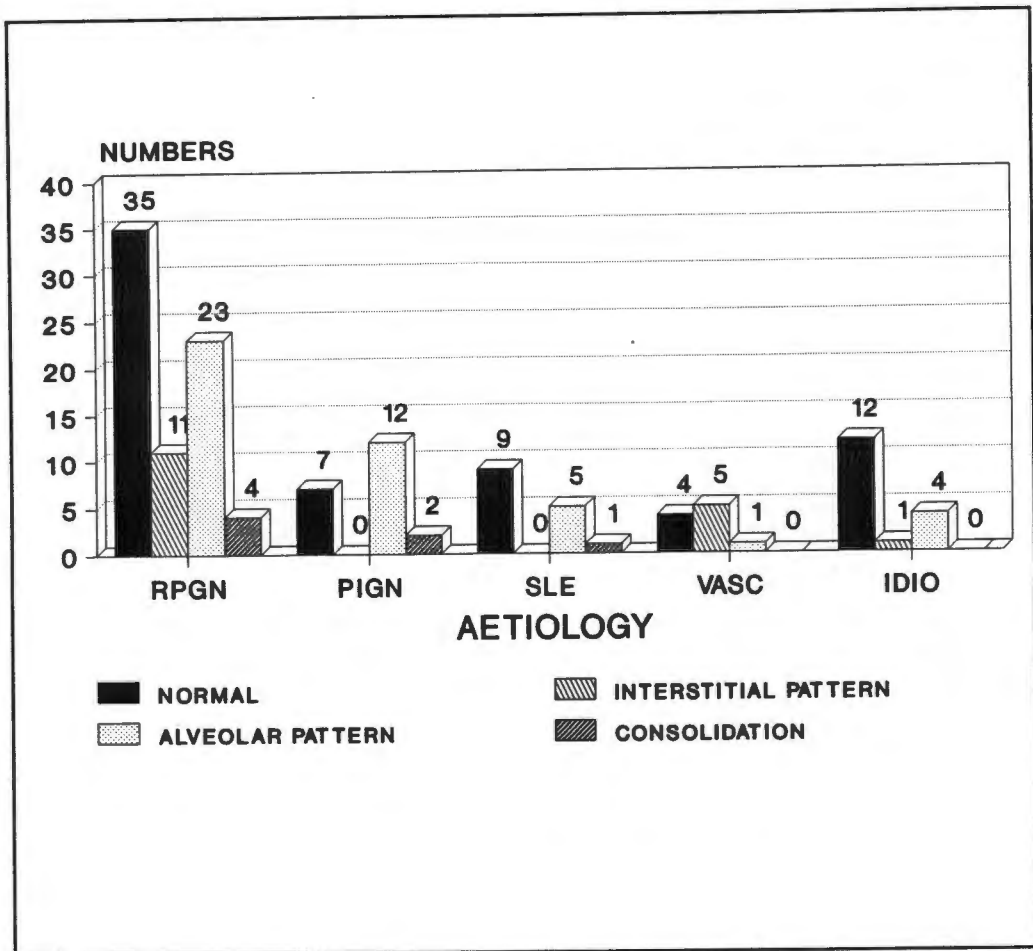


Figure 30: Chest radiographs on presentation in the total group and according to aetiology of RPGN

3.2.4 Histology

The blinded assessment of histology by light microscopy is demonstrated in figure 31.

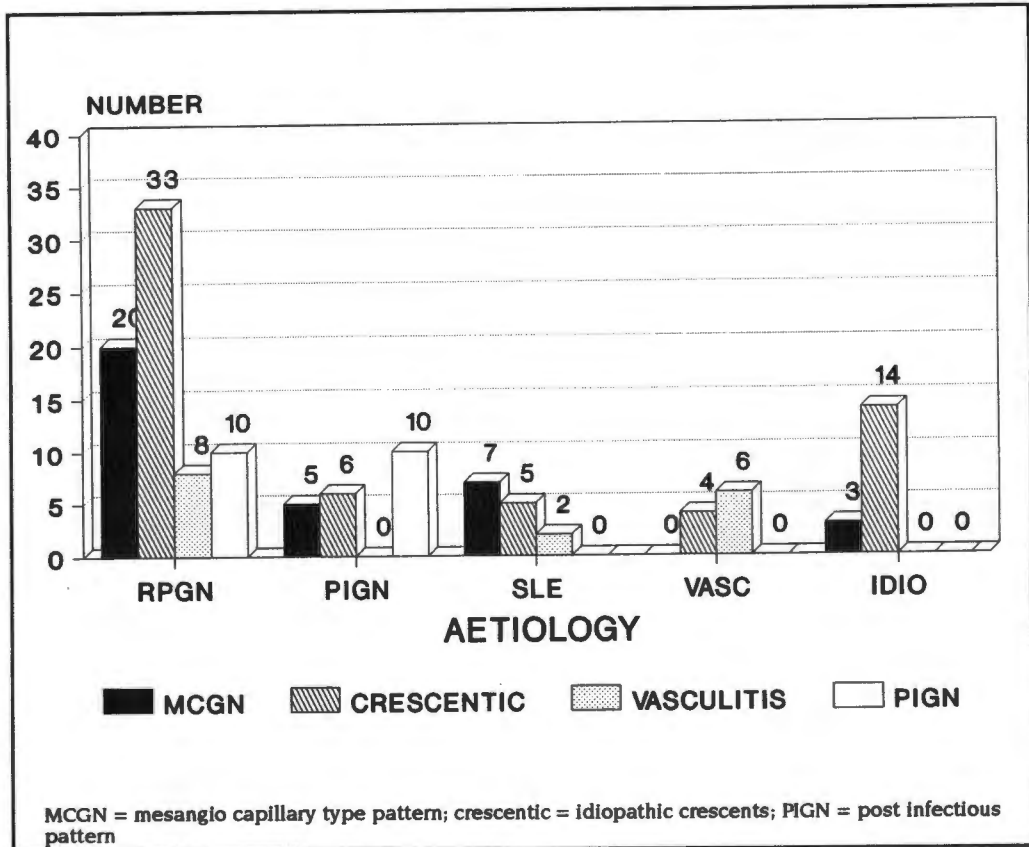


Figure 31: Histology on light microscopy in the total group and according to aetiology of RPGN

A SLE patient with membranous nephropathy and a patient with mixed membranous and MCGN in the RPGN group are not included. A high percentage of biopsies reviewed had the appearances of MCGN on light microscopy. Only four of these patients had a final clinico- pathological diagnosis of primary MCGN. Twelve patients had a final diagnosis of either SLE or PIGN and three were diagnosed as having idiopathic RPGN.

The number of crescents and their types are shown in figure 32.

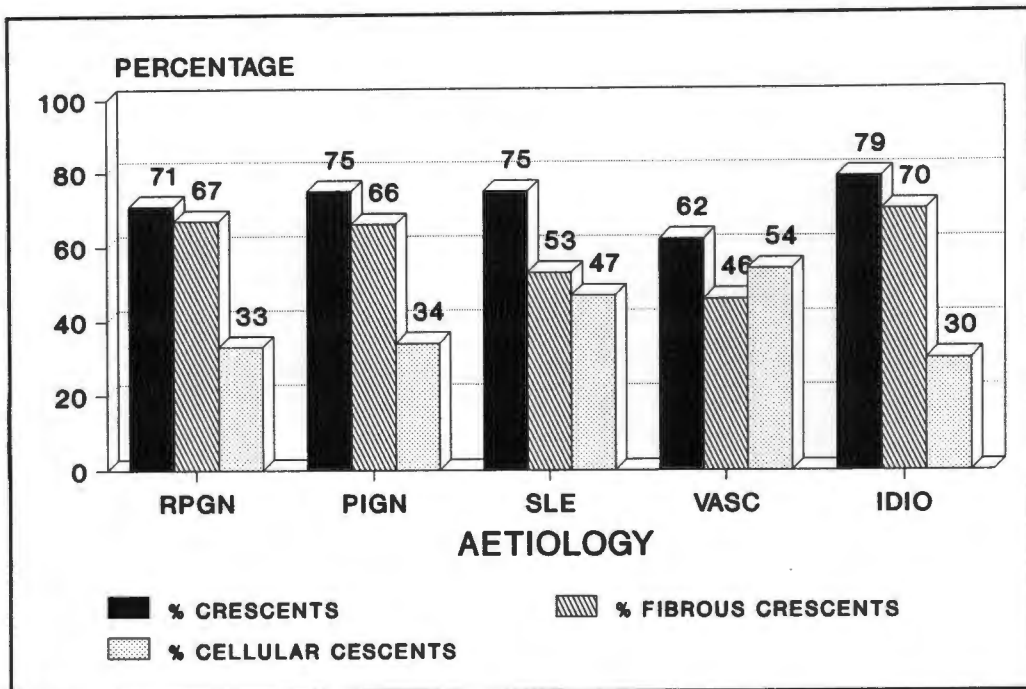


Figure 32: Percentage of crescents in the total group and according to aetiology of RPGN

Patients with crescents in excess of 80% are shown in figure 33.

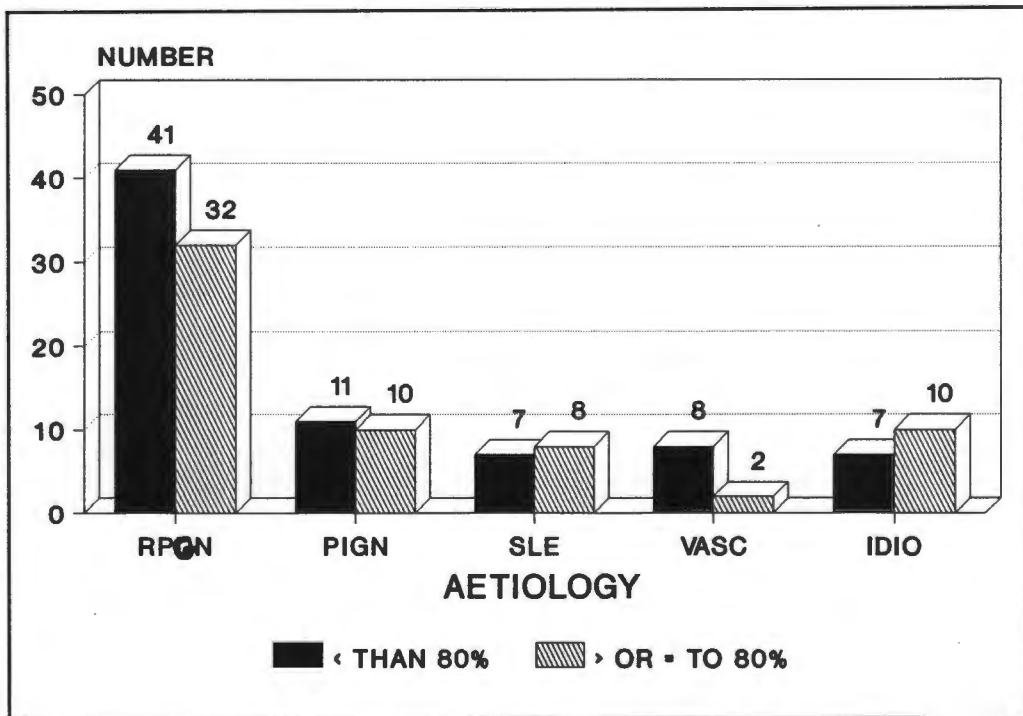


Figure 33: Patients with greater than 80% crescents in the total group and according to aetiology of RPGN

The rates of interstitial infiltration and acute tubular necrosis are demonstrated in figures 34 and 35.

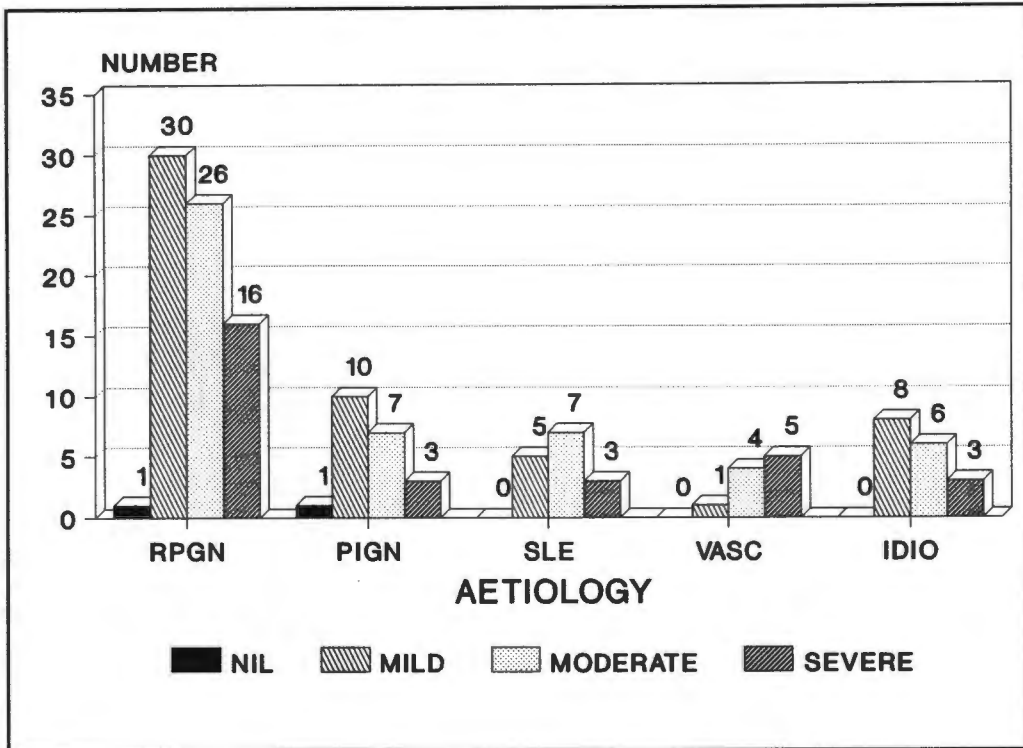


Figure 34: Incidence of interstitial infiltrate in the total group and according to aetiology of RPGN

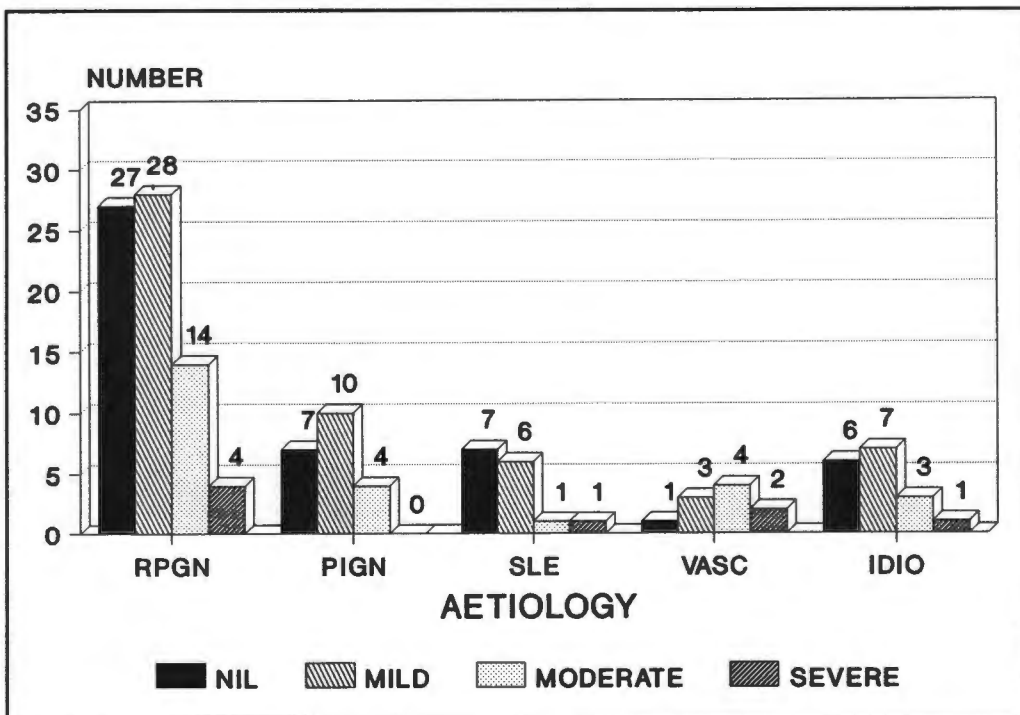


Figure 35: Incidence of acute tubular necrosis in the total group and according to aetiology of RPGN

Evidence of vasculitis and chronic interstitial changes are demonstrated in figures 36 and 37.

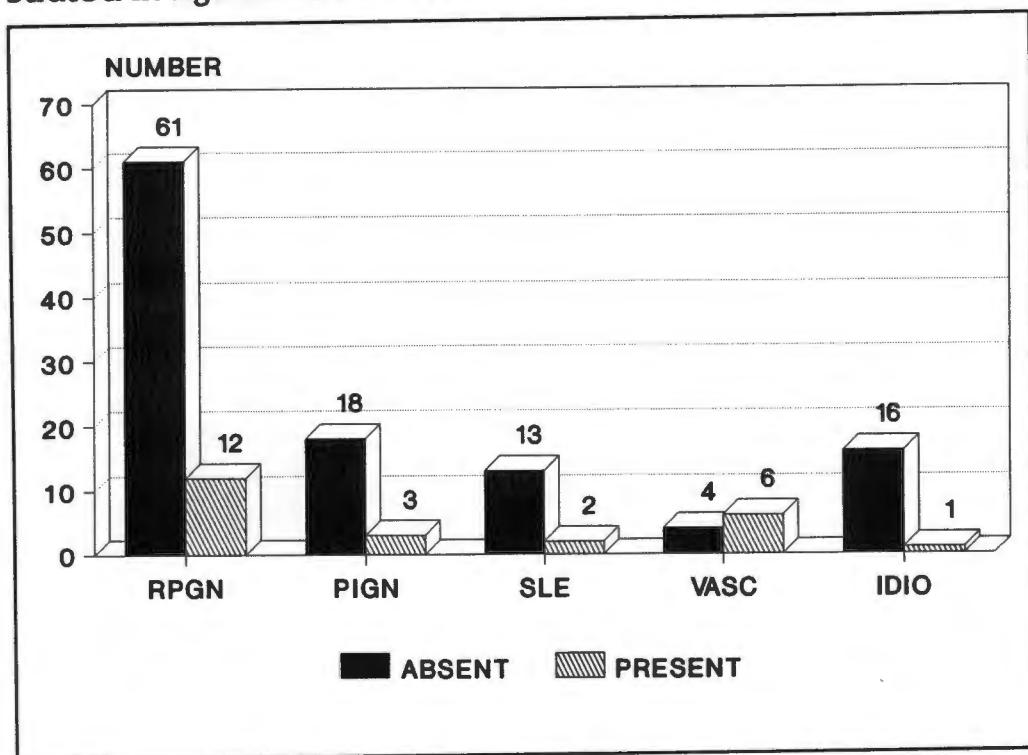


Figure 36: Incidence of vasculitis in the total group and according to aetiology of RPGN

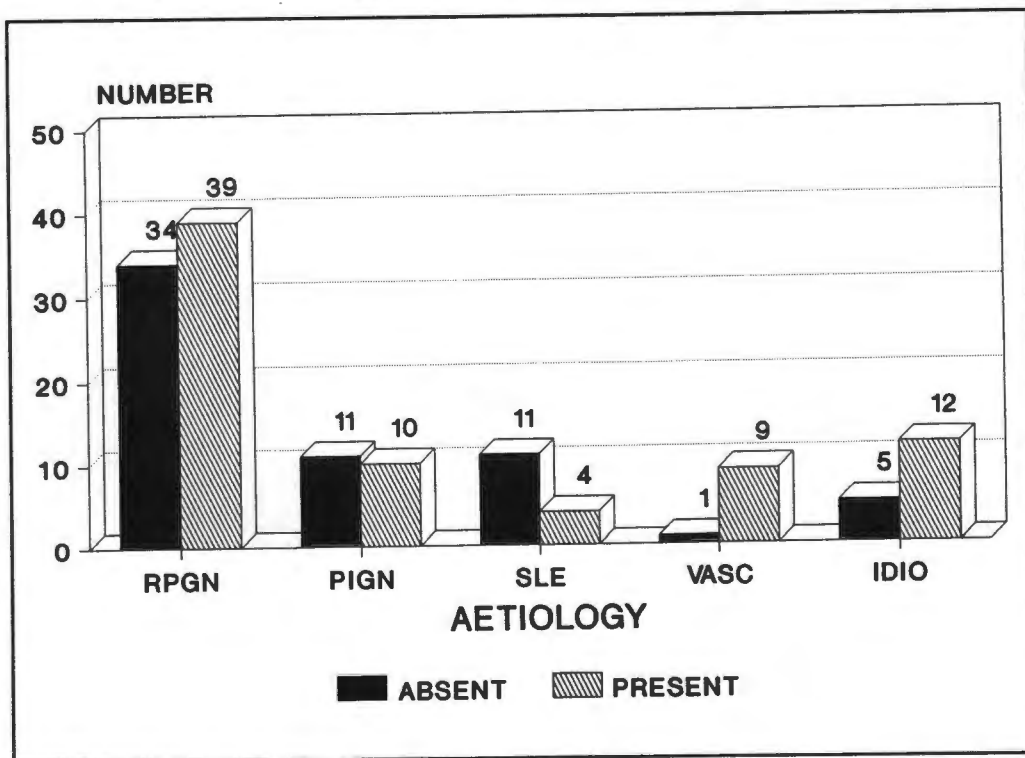


Figure 37: Incidence of chronic interstitial change in the total group and according to aetiology of RPGN

The incidence of hypertensive changes is shown in figure 38.

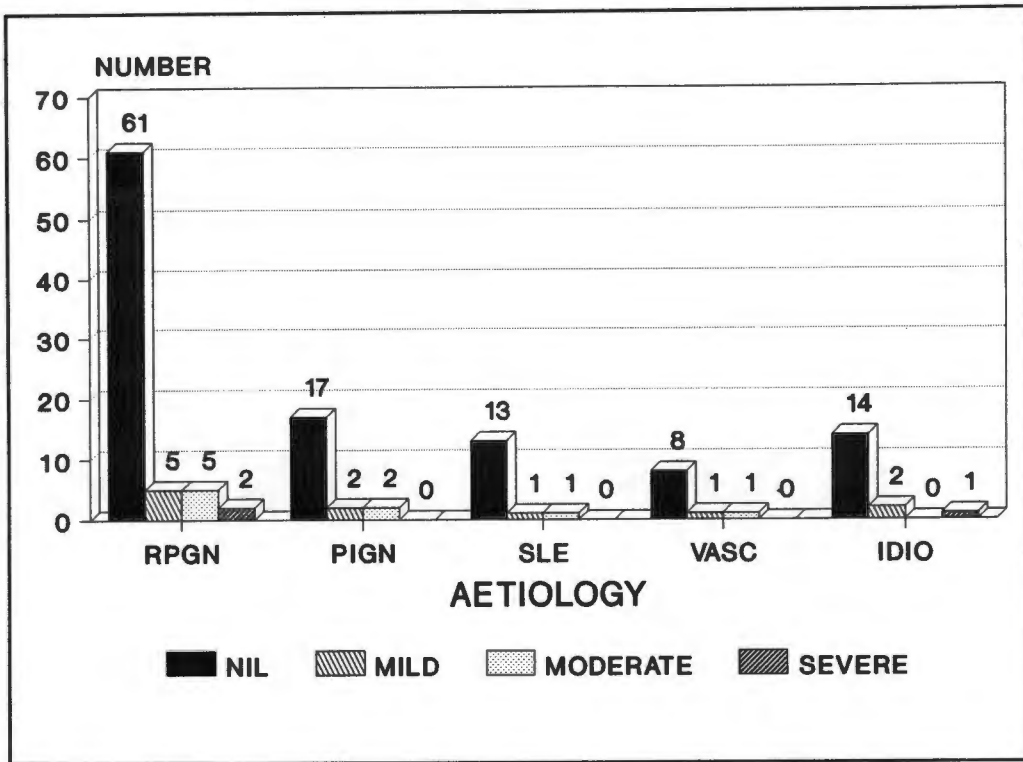


Figure 38: Incidence of hypertensive changes in the total group and according to aetiology of RPGN

Electron microscopy was especially helpful in the PIGN group where seven out of nine (78%) cases revealed subepithelial humps.

3.2.5 Prognosis and Treatment

Forty-five patients in the RPGN group were followed for less than one year. Of these, 16 patients were not accepted for long term dialysis and died from renal failure, two died from septicemia and one from the complications of SLE. Thirteen required long term dialysis and 13 improved sufficiently to not require renal replacement therapy. The five patients in the PIGN group followed for

less than a year did not recover renal function and were not accepted onto the renal program. Five patients in the SLE group were followed for less than a year. Two of these patients died prior to dialysis being instituted and three died shortly after long-term dialysis was commenced from infective causes. Only one patient in the vasculitis group was followed for less than a year and he has recovered function. Sixteen patients in the idiopathic group were followed for less than a year. Eleven of these patients remained in end stage renal failure and died, four required long term dialysis and one recovered function. Figure 39 demonstrates the follow-up time.

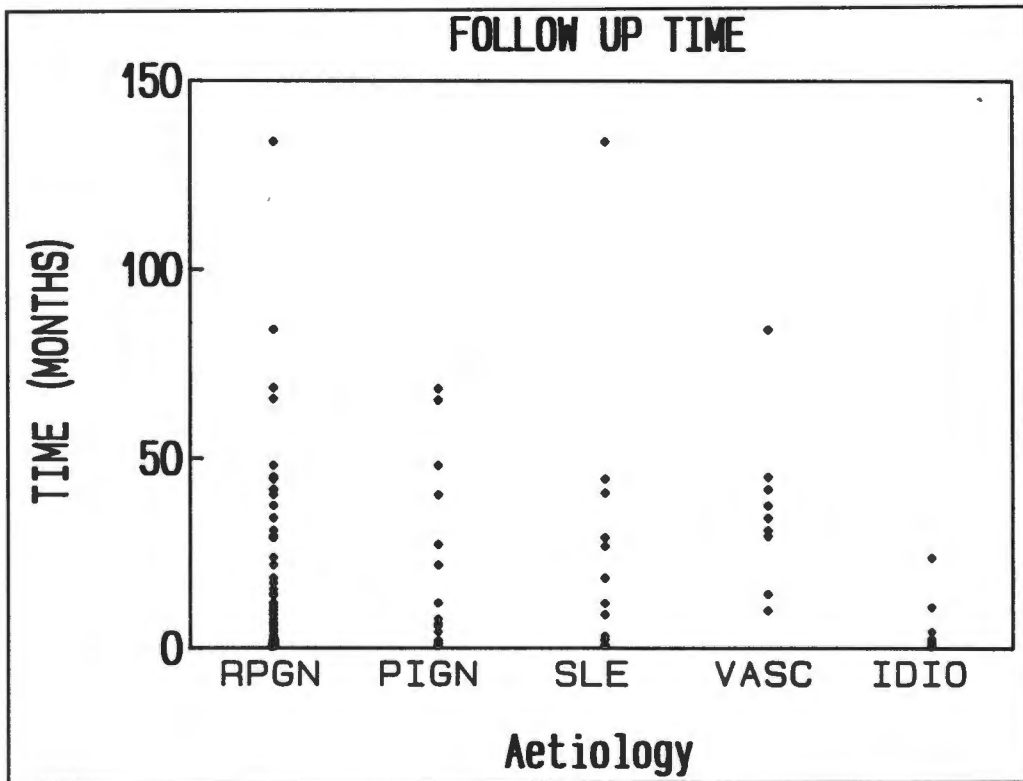


Figure 39: Follow-up time distribution in the total group and according to aetiology of RPGN

Length of time till death is demonstrated in figure 40.

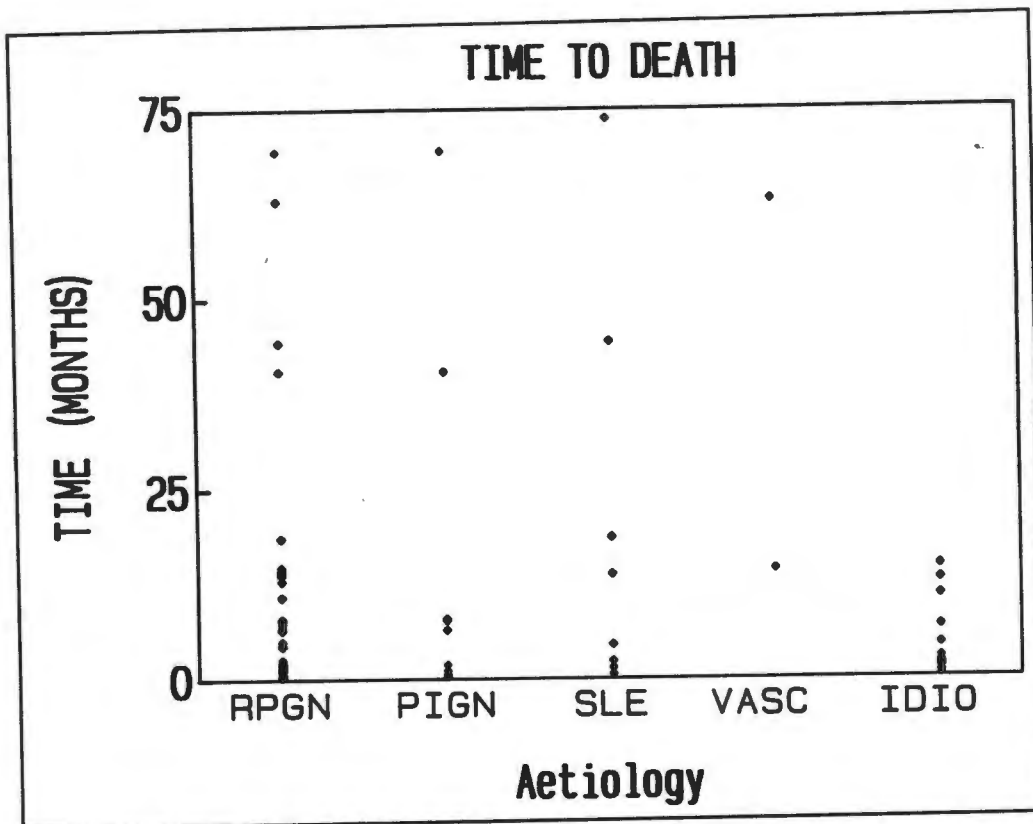


Figure 40: Time to death in the total group and according to aetiology of RPGN

Cause of death in the 36 patients who died during the study period is demonstrated in figure 41.

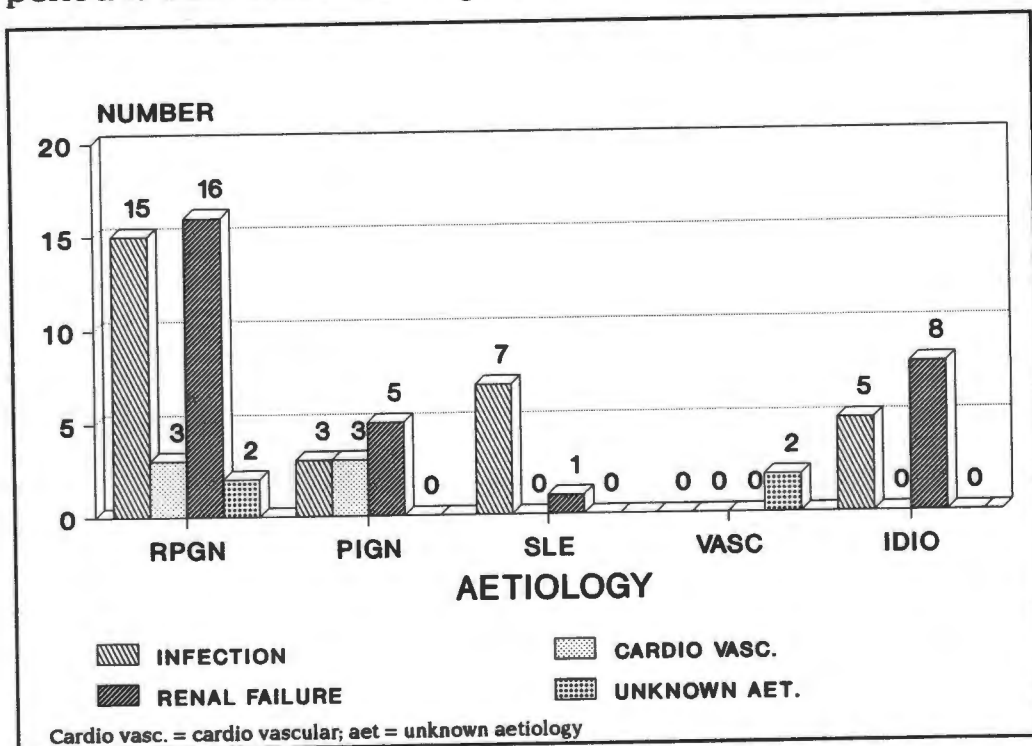


Figure 41: Cause of death in the total group and according to aetiology of RPGN

The modalities of therapy and the outcome of the various groups is demonstrated in figures 42 to 46.

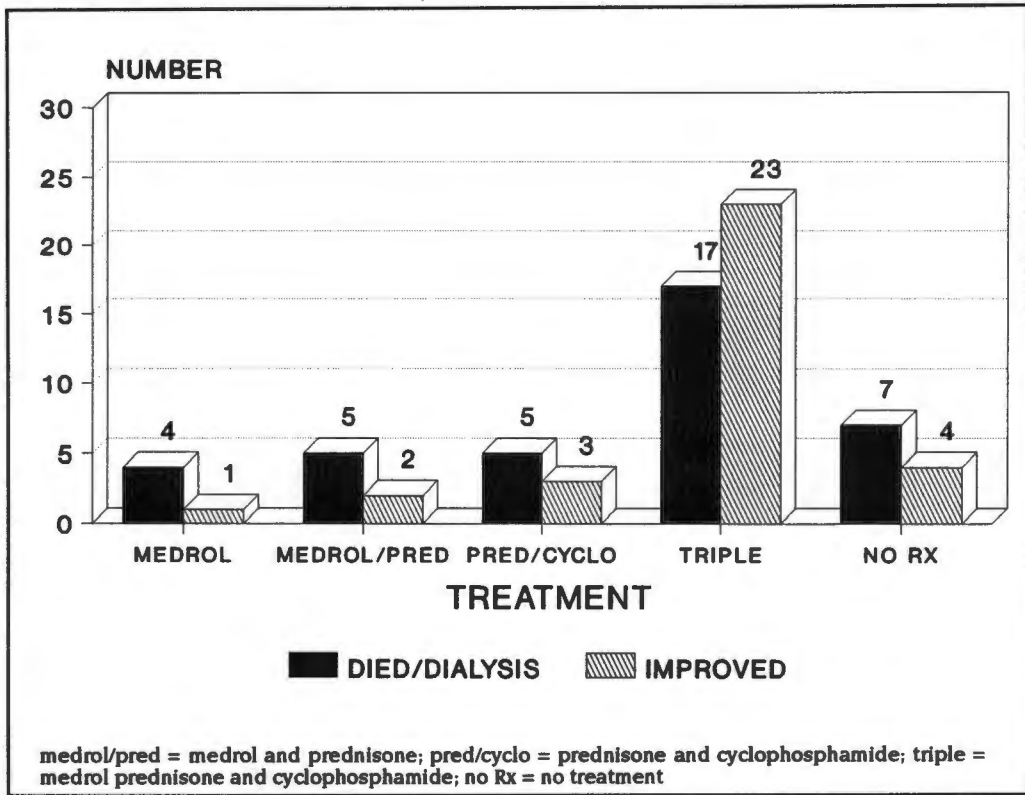


Figure 42: Treatment of the total RPGN group

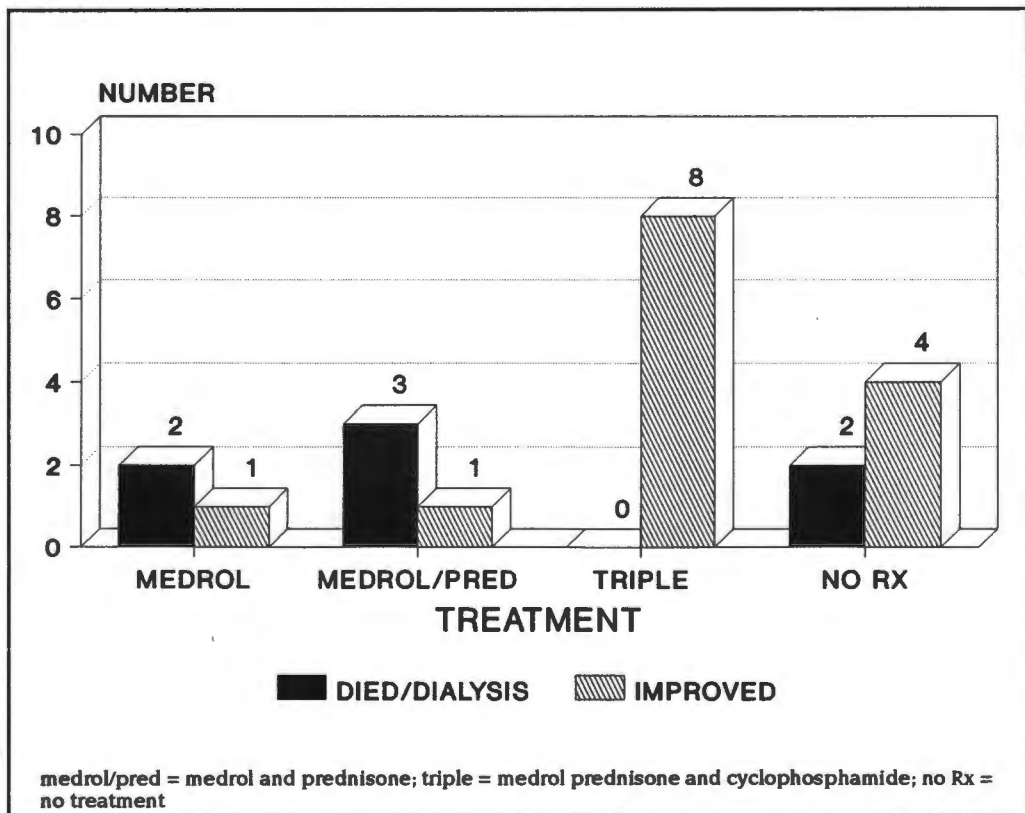


Figure 43: Treatment of the PIGN group

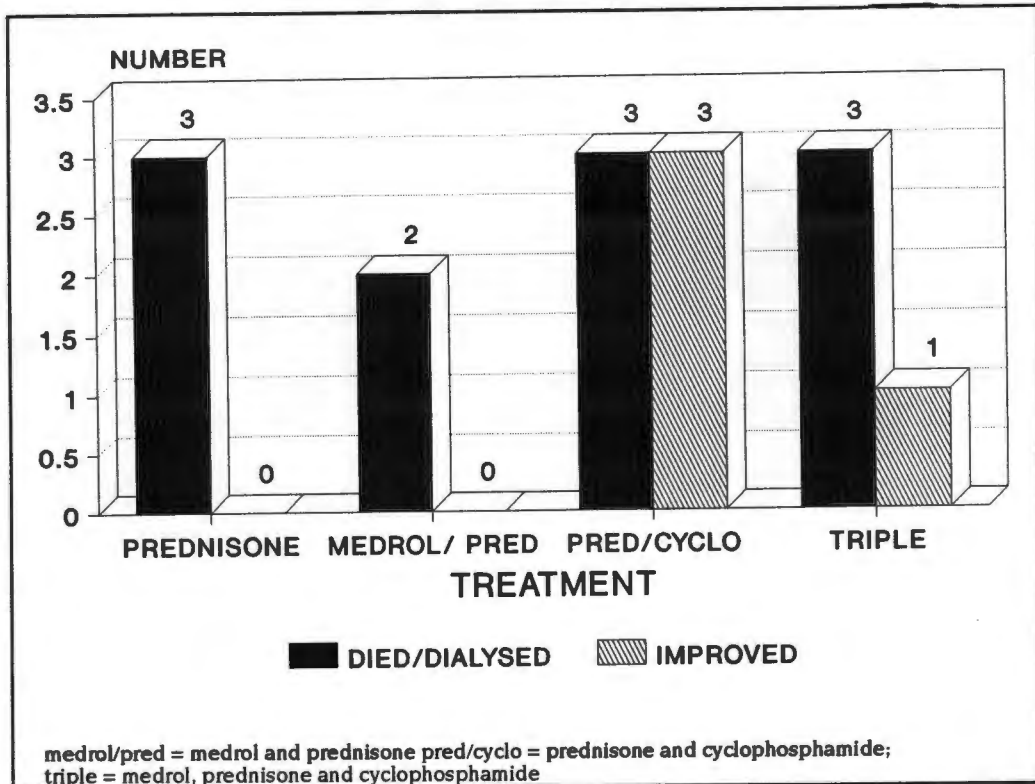


Figure 44: Treatment of the SLE group

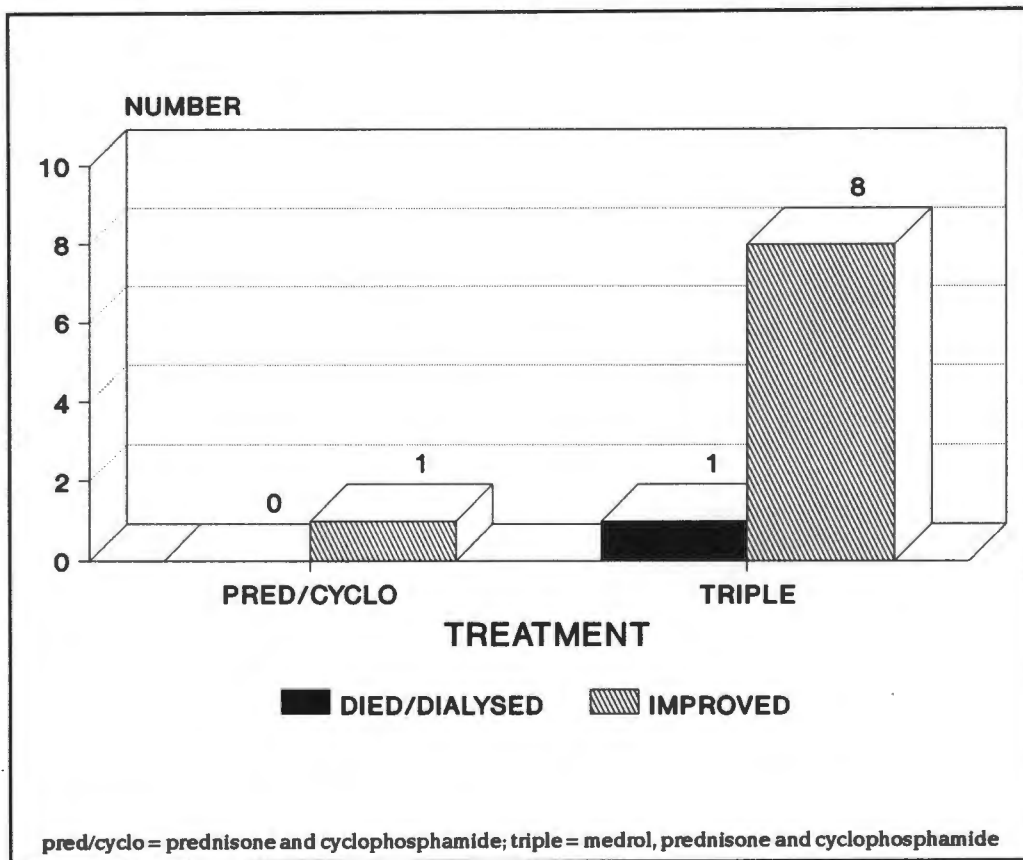


Figure 45: Treatment of the vasculitis group

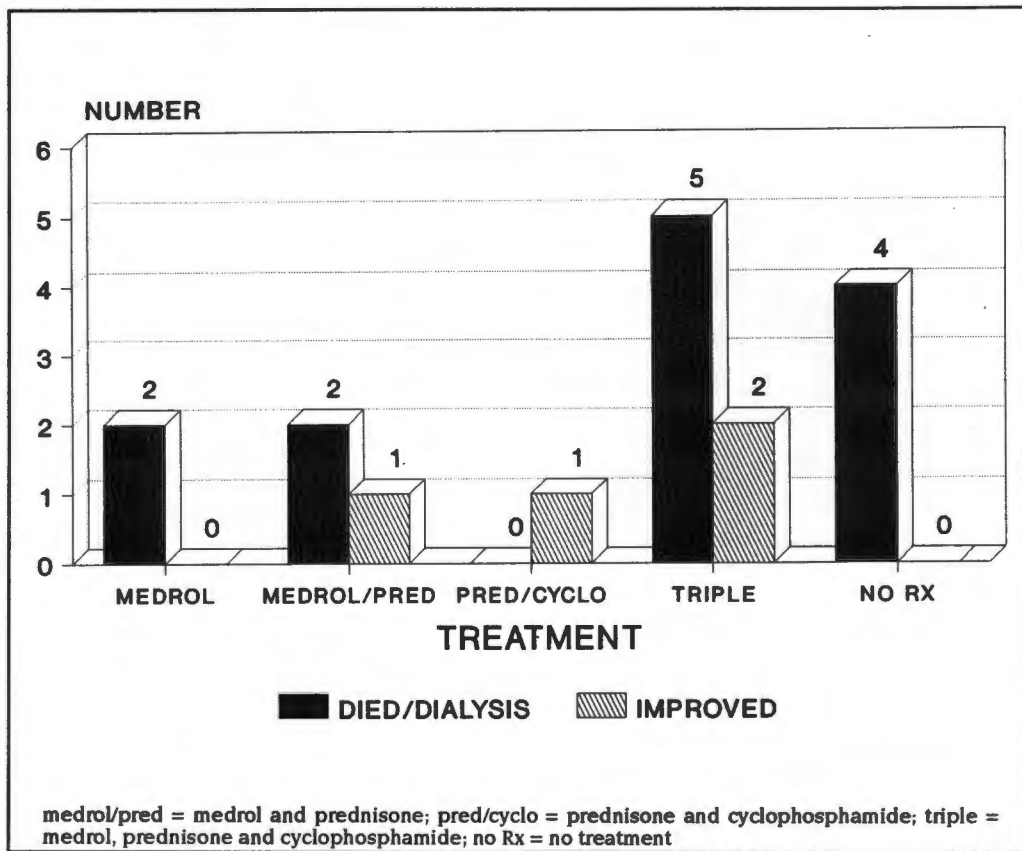


Figure 46: Treatment of the idiopathic group

The eight patients in the PIGN group treated with “triple” therapy recovered function. Two of the three patients treated with medrol only, three of the four treated with medrol and prednisone, and two of the four who received no therapy, died.

3.2.6 Prognostic Indicators

Oliguria was associated with a poor outcome. Seventeen of the 23 patients who were oliguric at presentation did not recover renal function ($p < 0.03$). This association was also significant for the PIGN group where six of the nine patients presenting with oliguria did not recover renal function ($p < 0.01$). The aetiology of RPGN had a significant correlation with outcome. Ten percent of the vasculitis group, 33% with post infectious GN, 77% with idiopathic

RPGN and 80% with SLE died or went into end stage renal failure as a result of their disease. The post infectious group had a significantly decreased mortality compared to SLE and idiopathic RPGN ($p < 0.01$). The vasculitis group also had significantly decreased mortality compared to SLE and idiopathic RPGN ($p < 0.01$). Fifteen of the 27 patients with a serum creatinine level below 500 $\mu\text{mol/l}$ and 18 out of 46 patients with a level above 500 $\mu\text{mol/l}$, at presentation, recovered renal function. This was not a statistically significant finding. Eighteen out of 40 patients with a creatinine clearance of less than 10 ml/min and 16 out of 29 patients with a creatinine clearance of greater than 10 ml/min at presentation, recovered renal function. This result was not statistically significant.

Patients with more than 80% crescents ($n=32$) had a poor prognosis with 14 deaths and eight surviving in end stage renal failure. This outcome was significantly worse than that in the group with 50% to 80% crescents ($n=37$) of whom seven died and nine survived with end stage renal failure ($p < 0.05$). Of the four patients with less than 50% crescents, all recovered sufficient renal function so as not to require renal dialysis. The severity of interstitial infiltrate had no prognostic significance.

Eight of the 28 cases with a "poor" prognosis on light microscopy did not progress to end stage renal failure. Fourteen of the 29 patients with a "good" prognosis on histology did not recover renal function ($p=0.03$).

4.0 DISCUSSION

4.1 INCIDENCE

The overall incidence of RPGN (3.8%) in this study was similar to the 2 to 7% reported in the literature (48). The aetiology of the syndrome however was unique to the Western Cape. The vasculitis and anti-GBM antibody disease groups were relatively uncommon and the incidence of RPGN associated with SLE was high in this study. We also report a high incidence of PIGN, in keeping with previous studies from developing countries (46,47). The true incidence of idiopathic RPGN was difficult to assess because of the ill defined nature of this group.

4.2 DEMOGRAPHIC FEATURES

The broad spectrum of disease aetiology probably reflects the population heterogeneity. SLE is common in the mixed origin group residing in the Western Cape. Whites constituted a high proportion of the vasculitis group of patients, in keeping with studies in Europe and America (6). The low incidence of anti-GBM disease may be due to the high proportion of the mixed origin and black groups. Low incidence of this disease in black patients has been previously reported (17).

The average age of 41 years was higher than that reported for the study in Durban (46) and similar to European and American studies (48,51). The average age in the PIGN group was 48 years, which was higher than that reported in other studies where the

disease has been described as affecting predominantly the young (46,47). In this study the age distribution for a post infectious cause of RPGN peaked between 20 and 30 years and then again above 50 years. This study did not include the paediatric population (below 12 years of age).

There was a male predominance in this study for all groups except for SLE where there was a 2:1 female to male ratio. Although the numbers in this subgroup were small (15 patients), the ratio is striking as SLE is predominantly a disease of women with a female:male ratio of 9:1. (118). Experience at GSH in 114 patients with biopsy proven SLE studied over a 10 year period showed a female to male ratio of 5:1 (119). The overall male predominance was in accordance with previously published studies (48).

The majority (62%) of patients were from the underprivileged community. Whites were the exception in the study where 80% fell into the good social class category. The high incidence of PIGN in the black and mixed group was probably due to poor socio-economic circumstances rather than racial differences.

4.3 CLINICAL PRESENTATION

The commonest presenting features were lethargy, upper respiratory tract symptoms and arthralgia, all of which were non specific in nature. The vasculitis group had the highest incidence of upper respiratory tract symptoms. This has been reported in other studies (61-66). The high incidence of arthralgia and rash in the vasculitis and SLE groups was related to the underlying disease

processes. All the patients in the anti-GBM group presented with haemoptysis. The small number of subjects prevented comparison with other studies. The incidence of haemoptysis in the vasculitis group (33%) was similar to reports elsewhere (61,62).

Oedema was more common than that reported in other studies and may reflect late presentation of the patients (46-48). About half of the patients had nephrotic range proteinuria. In these patients the relative role of renal failure and hypoproteinemia in the development of oedema could not be determined. The overall incidence of hypertension in this study was similar to studies elsewhere (51). The high incidence of hypertension in the idiopathic group may be due to the late presentation of patients with advanced renal failure and reflect fluid overload at presentation.

4.4 SPECIAL INVESTIGATIONS

Microscopic haematuria, proteinuria and urinary casts were usually present and did not help in differentiating between the various disease processes.

The overall incidence of macroscopic haematuria was similar to that reported in other studies (51). The proportion of patients with nephrotic range proteinuria, especially in the PIGN group and the SLE group, was high. The incidence in the idiopathic group (47%) was similar to that quoted in the literature (47,48,51,67,68).

The SLE and vasculitis groups tended to present with better renal function than the idiopathic and PIGN groups. The most likely cause for the difference between subgroups was the nature of the underlying pathology. Late presentation of the PIGN and idiopathic groups to hospital may have exaggerated this difference. The SLE patients were usually closely followed with a lower threshold for biopsy and were therefore diagnosed earlier.

Although anaemia was common to all the groups, it was most profound in the idiopathic and PIGN groups; again, delay may be the cause. A large number of SLE, PIGN and vasculitis patients had ESR values greater than 100 mm in the first hour, a well described feature in the literature (48).

Anti DNA antibody and anti nuclear factor assays in the SLE group was positive in about 70% of patients, which correlated well with the literature (71,91). Serological evidence of PIGN is reported to occur in 90% of patients tested serially (117). In this study 71% of patients had either a significant anti-streptolysin O titer or anti DNase B titer.

The high incidence of low complement levels was expected in the SLE and PIGN groups. C3 was more often depressed than C4 in the PIGN group. Complement levels in the vasculitis group were usually normal, an expected finding. The incidence of hypocomplementemia in the idiopathic group was unexpected and unexplained.

C3 appeared to be a more sensitive marker than C4 for hypocomplementemia in the PIGN group. Complement levels in the vasculitis group were usually normal, an expected finding. The high incidence of raised CIC levels in the SLE and PIGN groups was expected. The high incidence of raised CIC levels in the vasculitis group may be explained by secondary infections or other underlying diseases (70). Two (50%) of the anti-GBM group had hypocomplementemia which was not a feature noted in the literature (70).

C reactive protein was elevated in all cases of PIGN which confirmed the sensitivity of this assay. C reactive protein levels did not correlate well with the raised ESR levels in SLE patients, which is in keeping with other studies (74,75).

The value of ANCA in the assessment of RPGN cannot be determined from this study due to the small number of patients tested. It is, however, a serological investigation which will play a major diagnostic role in the future (30,32,84).

A large number of chest radiographs demonstrated an alveolar pattern in keeping with fluid overload. This was especially evident in the PIGN group and may be explained by late presentation of patients to hospital.

4.5 HISTOLOGY

A high percentage of biopsies had the appearances of MCGN on light microscopy, and this was particularly so in SLE. However only

20% of these patients had a final clinico-pathological diagnosis of primary MCGN. Fifteen percent of these patients were diagnosed as idiopathic RPGN, while the remaining patients were diagnosed as having either SLE or PIGN. Electron microscopy was not performed on the biopsies where idiopathic RPGN was originally diagnosed. These were thought to be primary MCGN on review, and the diagnosis might have been missed initially. In a high proportion of biopsies it was impossible to categorize the underlying cause of nephritis. These results reflect the difficulty in making a definitive diagnosis of the aetiology of the underlying nephritis on light microscopy.

There were no patients with idiopathic necrotising glomerulonephritis which, according to world literature, usually comprises a significant proportion of the idiopathic group (51).

The vasculitic group had a high incidence of severe interstitial infiltrate and this correlated well with literature reports (51).

Seventy one percent of the idiopathic and 48% of the PIGN groups of patients had chronic interstitial change which might be related to their late presentation.

The poor correlation between the high incidence of clinical hypertension at presentation and hypertensive changes on biopsy was similar to that reported in the literature (51).

Many biopsy specimens were not examined by EM or IF with a corresponding decreased diagnostic accuracy. The importance of electron microscopy was demonstrated by the fact that three

patients without typical histology of PIGN, as well as a patient with MCGN pattern on light microscopy, had “humps” on electron microscopy, suggesting the diagnosis of PIGN.

4.6 TREATMENT AND OUTCOME

This study has all the caveats discussed in the literature review. It was retrospective, had small numbers in each group, had no standardized therapy and was uncontrolled. The mortality or progression to end stage renal failure in this study was high (53%), especially considering that 21 of the 73 patients had PIGN, which was believed to have a better prognosis. Limited dialysis facilities as well as late presentation to hospital contributed to this high mortality.

Post infectious GN had a prognosis intermediate between the SLE and the idiopathic groups. The fact that all the patients who did not recover renal function in the PIGN group were considered unsuitable for the long term dialysis program was a reflection of their poor socio-economic status. This disease was not as benign in this population as reported by others in the literature (47,49,116). The fact that a significant number of patients with PIGN, with at least 50% crescents, recovered on “triple” therapy must be regarded with caution as it may be a reflection of the natural history of the condition. A prospective controlled randomised trial would be required to assess this modality of therapy adequately.

The prognosis in SLE was poor irrespective of the modality of therapy. The study was unable to indicate whether immunosuppressive therapy was beneficial. The high incidence of fatal infections may have been related to either the SLE and/or immunosuppression. Prognosis might be improved by modifying the immunosuppressive protocol or by abandoning aggressive therapy in patients suitable for the dialysis program.

The results of therapy in the vasculitic group were similar to those quoted in the literature (62,65,110). The deaths in this group were unrelated to the underlying vasculitis.

The idiopathic group had a high incidence (76%) of progression to end stage renal failure which was significantly different to the 35% quoted in the literature (117). The spectrum of the disease in this study differs to that reported in European and American studies where idiopathic RPGN associated with vasculitis confined to the kidney, is more prevalent.

4.7 PROGNOSTIC INDICATORS

The most significant prognostic factor was the underlying cause of the RPGN. Poor prognosis correlated with oliguria but with no other clinical factors or laboratory investigations, a finding reported elsewhere (51).

Histology predicted poor renal outcome when more than 80% crescents were found. Light microscopy was also helpful in prognosticating a good outcome in biopsies with less than 80% crescents.

4.8 CONCLUSION

The profile of RPGN in the population studied was unique due to the heterogeneous nature of the group. The high incidence of PIGN glomerulonephritis was probably related to the poor socio-economic conditions, while the high incidence of SLE was probably genetic. Interestingly, the female to male ratio seen in SLE was not apparent in this subgroup. Idiopathic RPGN appeared to be a different spectrum of disease to elsewhere and reasons for this are unknown. This group might have been better defined with earlier presentation to hospital and improved serological and histological investigations.

The study confirmed that the clinical features of RPGN were non specific and that the biochemical assessment of renal function was not a significant prognostic indicator of outcome.

Light microscopy alone was adequate to make the diagnosis of crescentic nephritis. However clinical features, serology, EM and IF were essential in making an aetiological diagnosis. Prognosis in patients with greater than 80% crescents is poor. In view of the subjective nature of light microscopic assessment, prognosis in patients with less than 80% crescents was unreliable.

The success of "triple" therapy in the vasculitic group confirmed results reported elsewhere. All the patients with PIGN treated with "triple" therapy recovered function but a prospective, controlled trial is required to confirm the efficacy of this modality of therapy.

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