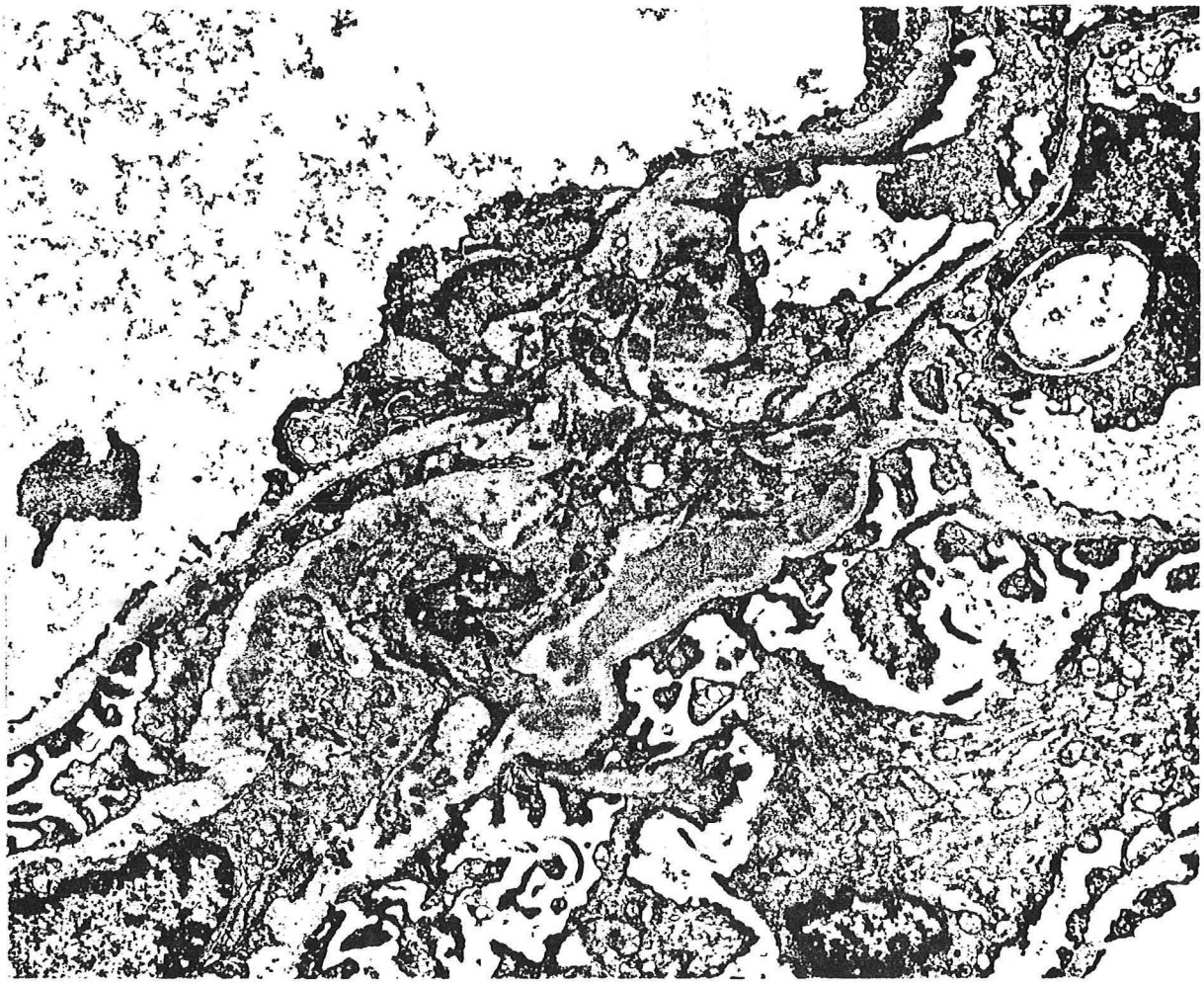
IGA NEPHROPATHY



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Introduction

The clinico-pathologic syndrome known as IgA nephropathy was first recognized in 1968 with the description by Jean Berger of 25 patients who had in common a history of recurrent hematuria and proteinuria. Renal biopsies of these patients revealed a unifying pathology of IgA deposition within the glomerular mesangium (1). Predating this description were several reports detailing what probably encompased Berger's disease. In 1914, Volhard described focal nephritis (2) and in 1960, Ross made the association of recurrent hematuria and focal glomerulonephritis (3). However, it was the unique contribution of Berger in noting, through the use of immunofluorescence studies, that IgA deposition was the unifying feature in the syndrome, and credit for the disease description is appropriately placed with Berger.

Clinically, the disease is manifested as recurrent hematuria (often in association with respiratory infections and exercise), proteinuria, and hypertension. Epidemiologically, the disease has a 3:1 male preponderance and incidence varies widely on a geographic basis. Despite earlier beliefs that Berger's disease was a relatively benign condition, it has been shown that up to 30% of patients so afflicted progress to severe degrees of renal insufficiency and eventually end-stage renal disease (4).

This discussion will include a comprehensive description of the disease, its pathology, proposed pathogenesis and current therapeutic regimens.

Before entering into a description of this disease of unknown pathogenesis and known refractoriness to treatment, a semantic issue must be discussed. Specifically, not all syndromes of hematuria and proteinuria associated with glomerular IgA deposition are Berger's disease. Shown in Table I is a classification of syndromes with these associated features (5).

TABLE I
CLASSIFICATION OF IGA NEPHRITIS

I. Primary
- Berger's Disease-IgA nephropathy
- Henoch-Schonlein purpura;

II. Secondary (known association)
- Hepatobiliary disease
- Cystic Fibrosis
- Celiac disease
- Regional enteritis
- Neoplasms:
  - Carcinomas of the lung and colon
  - Monoclonal IgA gammopathy
  - Mycosis fungoides
  - Non-Hodgkin's lymphoma
  - Mixed cryoglobulinemia
- Sjogren's syndrome
- Dermatitis herpetiformis
- Ankylosing spondylitis
- Systemic lupus erythematosus
- Infectious diseases:
  - Mycoplasma infections
  - Leprosy
  - Yersinia infection
- Pulmonary diseases:
  - Pulmonary hemosiderosis
- Polycythemia
- Properdin or C4 deficiency
- Thrombocytopenia
- Scleritis
- Dermatomyositis

(modified from Ref. 5)

As can be seen, a number of disease processes have in common the triad of mesangial IgA deposition, proteinuria and hematuria. Although there was (and is) a movement by some investigators to view a number of these associations as a common disease process, the major trend is toward the view, first espoused by Berger, that a distinct disease does exist in which the sole clinicopathologic manifestation is IgA nephropathy. Indeed, Berger specifically excluded patients from his initial description which had known underlying diseases such as systemic lupus erythematosus, Henoch-Schoenlein purpura and liver disease (1). This discussion will thus center upon the primary form of the disease, IgA nephropathy or Berger's disease.

Pathology

The diagnosis of Berger's disease absolutely depends upon the demonstration, by immunofluorescence, of the presence of mesangial IgA in renal biopsy specimens (1); alterations in serum IgA levels or clinical findings are insufficient to make the diagnosis (6). It is thus appropriate to review the characteristic biopsy findings of this disorder.

Shown on the next page (Figure 1) is a schematic representation of the normal glomerular mesangium and the mesangium in Berger's disease. The mesangial cells are surrounded by a matrix, which serves to provide the architectural support for the capillary tuft. It is this matrix which is the target site of IgA deposition. The matrix itself is composed, in part, of types IV and V collagen, fibronectin, laminin, as well as a variety of ill-defined antigens (MBM10, MBM12) which are reproducibly stained by monoclonal anti-mesangial matrix monoclonal antibodies (7).

By immunofluorescence, anti-IgA antibodies reveal a staining which appears to globally involve the mesangium in a granular pattern (8), as shown in Figure 2.

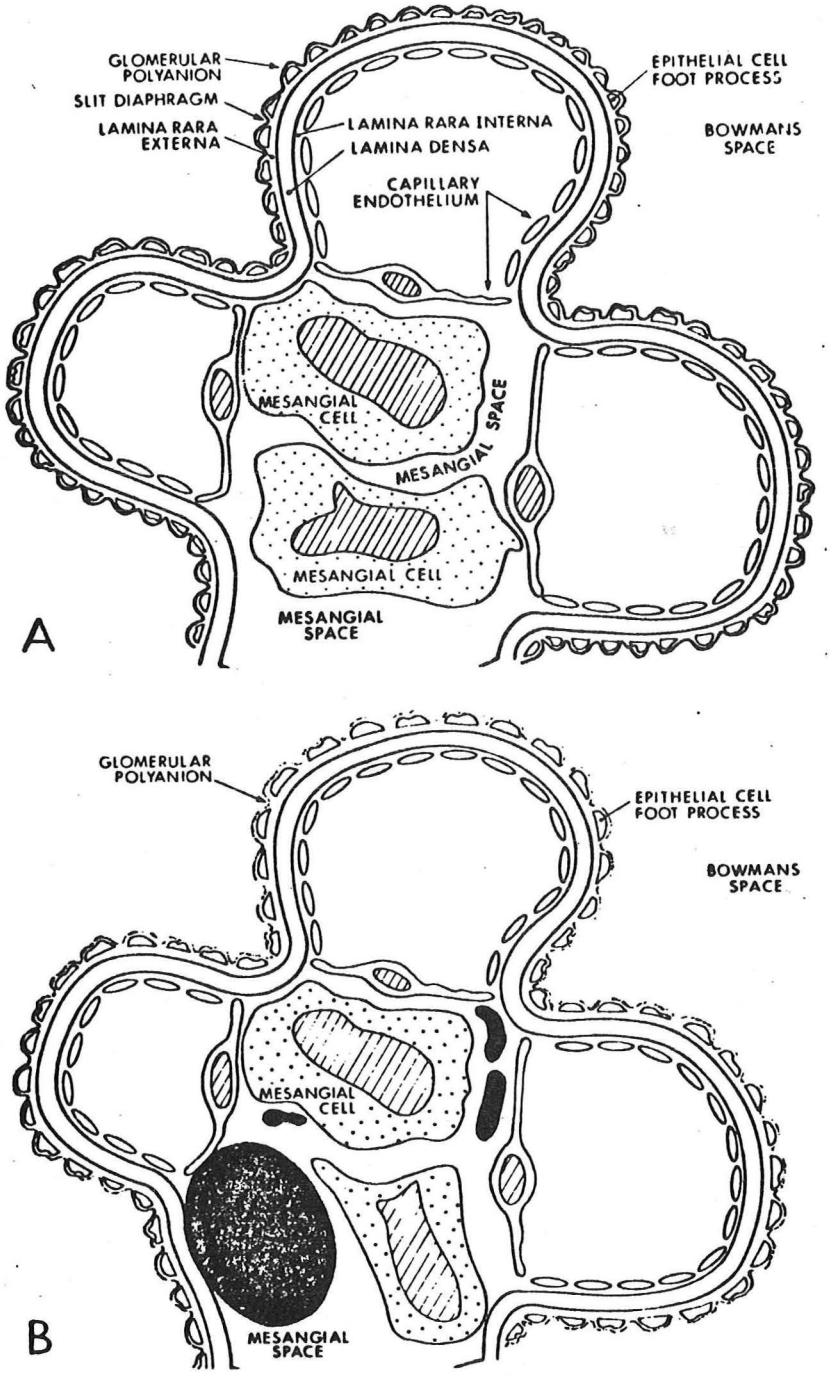


Figure 1: Schematic diagram of normal glomerular mesangium (A) and of mesangium in Berger's disease (B).

Figure 2: IgA deposition in a single glomerulus, as demonstrated by immunofluorescence.

It has now been determined, through use of high quality anti-IgA antibodies, that IgA_1, rather than IgA_2 is the subclass deposited within the matrix (8,9). Although the capillary walls are most often devoid of IgA deposition, this phenomenon has been noted in several instances (10,11), and such a finding is felt to reflect a more severe clinical course (12).

Other immunoglobulins as well as complement components frequently coexist with IgA in the glomerular mesangium of patients with Berger's disease (13,14). Shown in Table II is a list of biopsy findings which catalogues these other factors.

TABLE II

IMMUNOFLUORESCENCE FINDINGS IN IGA NEPHROPATHY

IgA only	27%
IgA + IgG	36%
IgA, IgG, + IgM	24%
IgA + IgM	13%
C_3	95%
Clq/C4	10-15%

(modified from Reference 3)

Again, a consistent feature is IgA, which can appear alone (14,15) or in association with IgG or IgM. C_3 deposition is a near universal finding (14). Components of the early classical pathway (Clq and C4) are unusual findings, whereas properdin can be demonstrated in 50-100% of biopsy specimens, suggesting that the alternate pathway of complement activation may play a role in the pathogenesis of the disease (16,17). The pattern of C_3 deposition closely parallels that of IgA (14).

Although immunofluorescence in evaluation of renal biopsies is the critical test in demonstrating IgA nephropathy, varying degrees of glomerular destruction, ranging from diffuse mesangial hypercellularity (18,19) to widespread sclerosis and crescent formation (20) have been observed by light

microscopy. Such changes are to be expected in a glomerulopathy which can potentially culminate in end-stage renal disease. There are no characteristic lesions noted by light microscopy, reflecting that the glomerulus can react to a variety of injurious agents in only a limited number of ways. [Notable in this regard is the fact that IgA deposition seen in secondary causes of IgA nephritis is indistinguishable from the pattern observed with Berger's disease (21,22).] Listed in Table III are some of the major patterns of glomerular damage noted in IgA nephropathy.

TABLE III

CHANGES IN THE KIDNEY OF PATIENTS WITH IGA NEPHROPATHY

Normal/essentially normal glomeruli
Diffuse mesangial hypercellularity
Focal/segmental mesangial hypercellularity
Glomerular adhesions
Glomerular capillary wall thickening
Focal glomerulonephritis
Crescentic glomerulonephritis
Minimal change nephrotic syndrome
Membranoproliferative (mesangiocapillary) pattern
Focal sclerosis
Membranous glomerulonephropathy
Increased lobulation of glomerular tufts
Tubulointerstitial changes
Vascular changes

[modified from Silva (5)]

By electronmicroscopy, 97% of biopsy specimens obtained from patients with IgA nephropathy reveal mesangial deposits (23,24) and occasionally subepithelial (25) as well as subendothelial deposits (26) are observed.

IgA

Because deposition of IgA within the glomerulus is the sine qua non for diagnosis of Berger's disease, certain features of this immunoglobulin require

review. Normally, IgA constitutes the second most prevalent serum immunoglobulin, and is usually about 10% of total immunoglobulin levels (27). In contrast, as shown in Figure 3, IgA represents the major immunoglobulin present in external secretions (28).

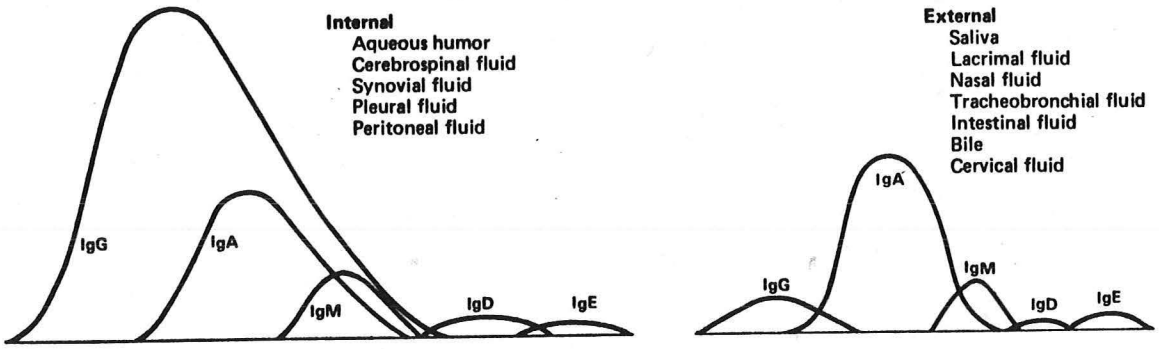


Figure 3: Immunoglobulin profile of internal and external secretions.

Two isotypes of IgA, IgA_1 and IgA_2 exist in man. IgA_1 is largely restricted to serum, whereas IgA_2 is the predominant form found in secretions (28). IgA can exist as either a monomer (i.e. 2 heavy chains and 2 light chains) or as a dimer composed of two monomers which are held together by disulfide linkage by a distinct moiety, the J chain (29,30). Shown in Figure 4 is a representation of such a linked dimer.

In addition, another polypeptide, secretory component (SC) is attached to IgA present in secretions, and it has been suggested that this component inhibits proteolysis of the immunoglobulin (29). Recently, an exciting set of experiments (see Ref. 31 for review) demonstrated that secretory component, produced by secretory cells, such as the hepatocyte, is inserted into the plasma membrane where it serves as a receptor for polymeric IgA. After binding and internalization of the SC IgA polymer complex, the entire product is secreted. Shown in Figure 5 is a schematic representation of this process.

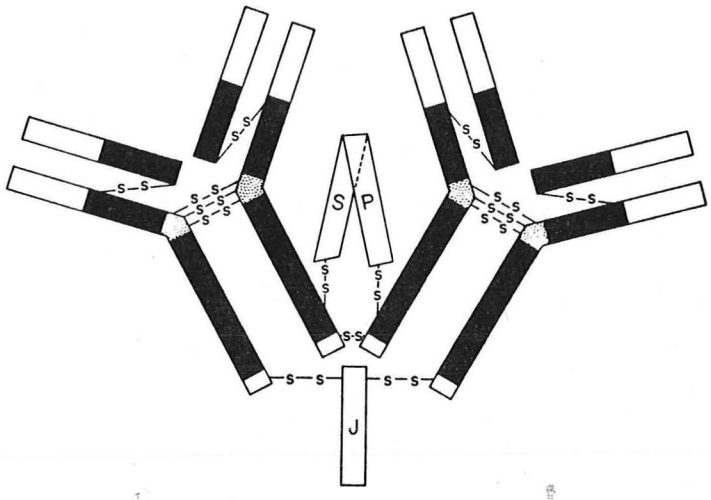
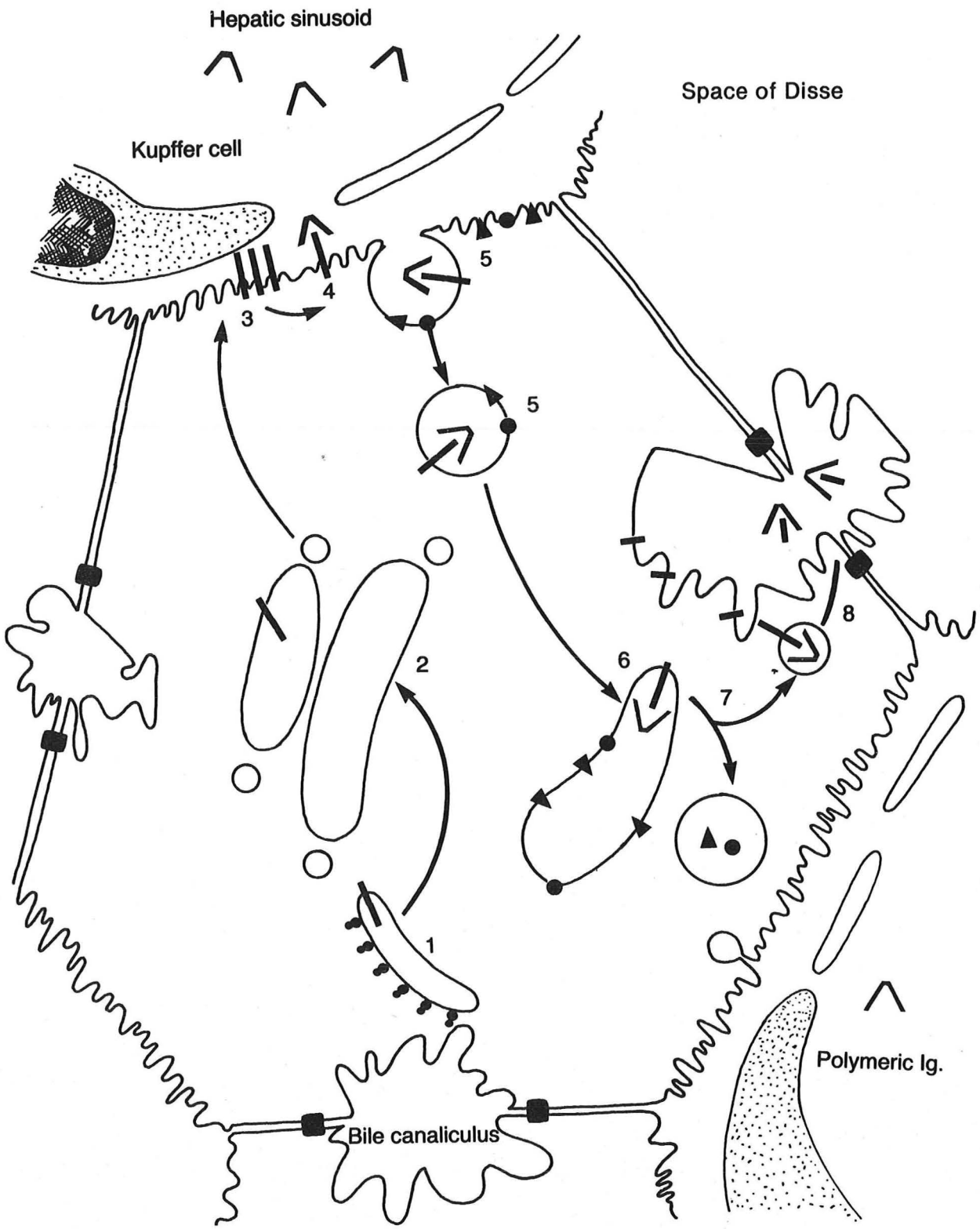


Figure 4: IgA dimer, with covalently linked secretory piece (SP) and J piece (J). From Ref. 30.

Although, as will be discussed, much attention has focused upon the possible role of the IgA-SC complex as a cause of IgA nephropathy, most recent studies indicate that the type of IgA found in mesangial deposits is IgA_1 (11).

In this regard, it has been demonstrated that circulating IgA_1 can exist as complexes (i.e. dimers and higher orders of polymerization) and these complexes are synthesized by plasma cells of spleen and bone marrow, in contrast to the site of IgA_2 synthesis and dimerization, which is localized to plasma cells in apposition to secretory epithelia (32). The possible role of IgA_1 polymers in the pathogenesis of Berger's disease is discussed below.



Proposed routing of secretory component in the rat hepatocyte.

1. Synthesis and core-glycosylation of membrane secretory component (SCm) in the rough endoplasmic reticulum. 2. Terminal glycosylation of SCm in the Golgi complex. 3. Transport of SCm from the Golgi to the sinusoidal plasma membrane via a route as yet undetermined. 4. Polymeric immunoglobulins (∧) present in the hepatic circulation bind to SCm on the sinusoidal plasma membrane. 5. Polymeric immunoglobulins bound to SCm are endocytosed in coated vesicles along with other receptor ligand complexes (▲●). 6. Endocytic vesicles fuse with the compartment of uncoupling of receptor and ligand, where receptor sorting occurs. 7. SCm and its ligand are transported to the bile canalicular plasma membrane whereas other ligands may be transported to lysosomes. 8. Upon cleavage of the membrane anchoring domain of SCm, the polymeric immunoglobulin bound to the extracellular domain of the receptor is released into the bile.

Pathogenesis of IgA Nephropathy

Although the pathogenic mechanism leading to Berger's disease remains unclear, certain known features of the disease have resulted in three lines of investigative efforts, namely examination of host factors, environmental factors and primary immunologic mechanisms.

Key features of Berger's disease, which lend insight into its pathogenesis, are shown in Table IV.

TABLE IV

FEATURES ASSOCIATED WITH IGA NEPHROPATHY

WHICH SUGGEST PATHOGENESIS

1. Frequent recurrence after renal transplantation
2. Rapid disappearance of IgA deposits from affected kidneys used for transplants
3. High prevalence of DR4 antigen
4. Increased levels of serum IgA polymeric IgA, and circulating immune complexes

(Modified from Ref. 33)

A. Epidemiology

It is evident that the apparent distribution of IgA nephropathy varies widely on a geographic basis. As shown in Table 5, Berger's disease is one of the most common forms of glomerulopathy in France, Spain, Italy, and Japan; indeed, it has been described as the most common form of glomermulonephritis in Australia. In contrast, much lower incidence has been reported from the United States and from Germany and other European countries (14).

TABLE V

INCIDENCE OF IGA NEPHROPATHY

Country	% of All Biopsied Patients with + Immunoflourescence for IgA
Singapore	33.7
Japan	28-35
France	18-22
Spain	11-20
Australia	12-18
Italy	15.9
Scandanavia	7-14
England	4
Canada	4
United States	1.5-5

[Modified from D'Amico (14)]

While this might immediately suggest that there is an environmental or genetic predisposition, it is important to recognize that disease recognition may play an equally important, if not dominant role in this disparity in geographic prevalence. Berger has suggested that the widespread practice of urinalysis in France might account for the relative high prevalence in this country (33). In addition, increasing use of immunoflourescence and higher quality immunoreagents has likely heightened sensitivity to detection (34) as illustrated in Figure 6.

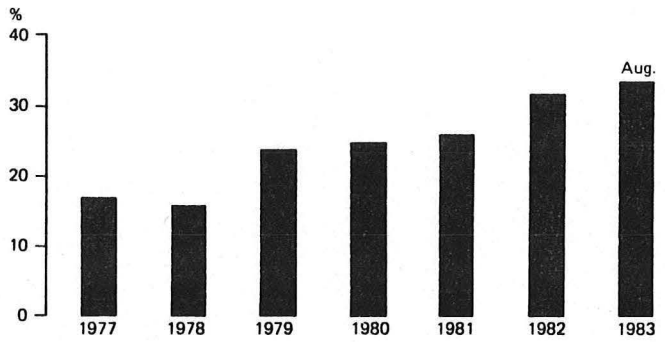


Figure 6: Incidence of primary IgA nephropathy among primary glomerulonephritides in the period 1977-August 1983.

It is clear, however, that some ethnic differences in disease occurrence are real. Incidence of IgA nephropathy amongst blacks is very low compared with the incidence observed in caucasians of the same area of study. In addition, the demonstrated male predilection for development of Berger's disease (male:female:3:1) provides further support for host factors in pathogenesis (4).

B. Host Factors

One possible explanation for the differences in disease prevalence on a world-wide basis is that of genetic immunosusceptibility. Investigations of this issue have focused upon: 1) HLA related predisposition, 2) differences in complement phenotypes, and 3) more direct genetic mechanisms.

Shown in Table VI is a compilation of HLA associations noted in several studies. Worldwide, there seems to be no consistent HLA type associated with the disease, although in France HLA BW35 has been found in 48% of patients with severe forms of the disease, as opposed to a rate of 19% in normal controls (35). In addition, an increased coincidence of IgA nephropathy and D4 has been noted (33). However, given the overall lack of finding of a particular HLA group it appears that if an HLA predisposition does exist, it is not a primary cause, but rather, may simply serve to facilitate aggravation of a process of HLA-independent origin. The possible role of complement phenotypes is even less clear. While several studies have indicated certain associations of complement phenotype (such as C3 fast alleles((36,37), the available evidence in support of this notion is meager and, *in toto*, unconvincing.

In contrast to HLA-mediated predispositions to Berger's disease, isolated reports (38,39) of affected kindreds suggest the possibility of a direct

TABLE VI

HLA SYSTEM AND IGA NEPHROPATHY

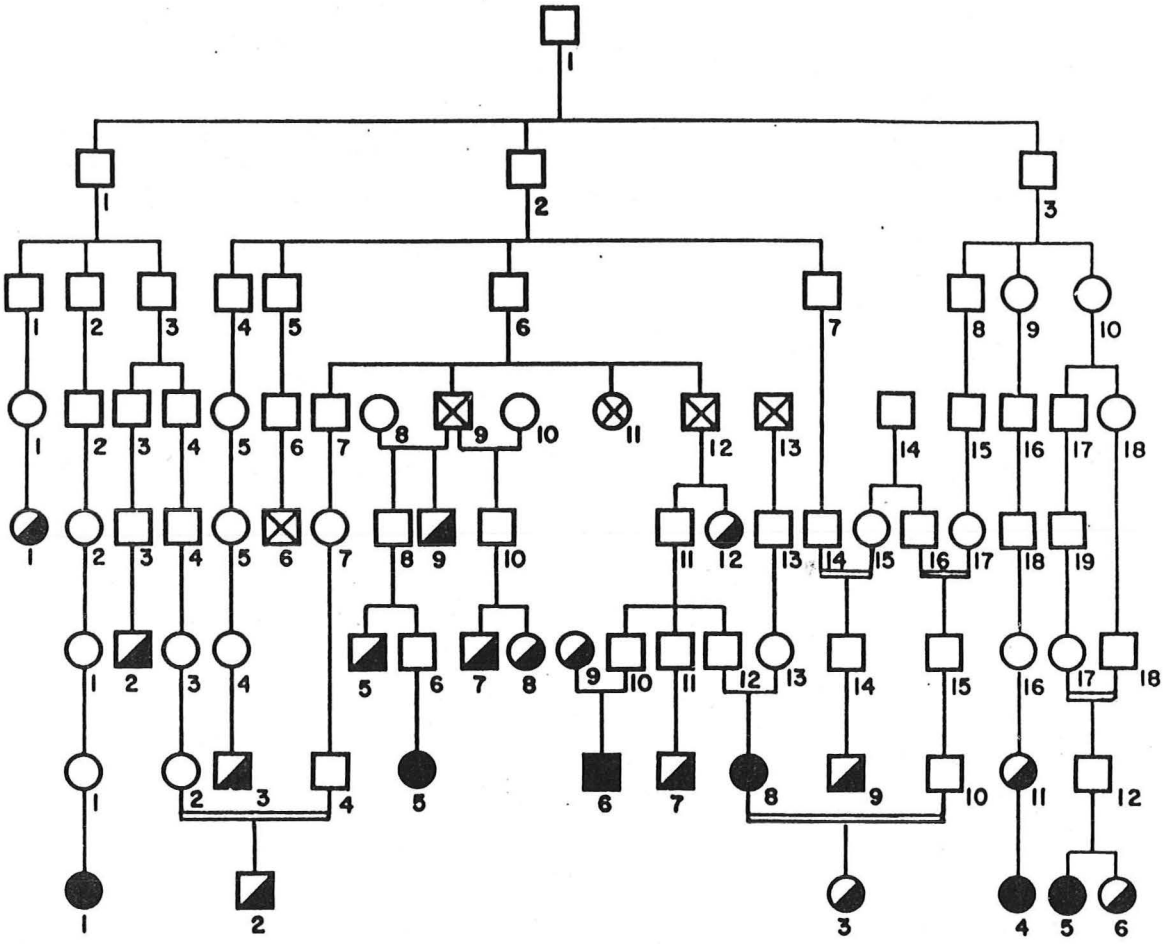
No HLA Associations Noted	Some HLA Associations Noted	
Italy	BW35	France
Spain	DR4	France
Finland	Cw1	Great Britain
Hungary	B12	USA
Singapore	BW35-DR7	USA
Australia	DR4	Japan
France	DEn	Japan
Japan	BW35	Australia
Great Britain		

[Modified from D'Amico (14)]

genetic mechanism in disease pathogenesis. Shown in Figure 7 is such a pedigree analysis. Notable is the loss of the usual male predilection to disease development. HLA analysis is meaningless in such a study, given the inherent distortion governed by direct inheritance, and unfortunately, insufficient analysis of such kindreds has been performed to provide insight into pathogenesis.

C. Environmental Factors

Given the unique physiologic role of IgA in providing an external barrier to infection, numerous investigators have focused upon the possible role of occult or overt infection, as well as dietary agents, in the pathogenesis of Berger's disease (18,39,40). Underscoring this contention is the well-described phenomenon of infection associated hematuria in patients afflicted with the disorder (4). Shown in Table VII is a list of precipitants to hematuria, and as can be seen, infections, particularly gastrointestinal and



. Pedigree of Patients with IgA Nephropathy in Eastern Kentucky Who Were Descended from a Single Person.
Squares denote male sex and circles female sex; ■ and ● indicate biopsy-proved IgA nephropathy; ◪ and ◒ indicate clinical glomerulonephritis; ⊠ and ⊗ indicate that "chronic nephritis" appeared on the death certificate; and ☐—○ indicates that a common ancestor is known for the spouses in the marriage.

Figure 7

respiratory, account for the vast majority of such episodes. This issue remains clouded because most investigators have failed to find any apparent association between antigens derived from infectious agents and IgA nephropathy, and in those instances where such associations have been demonstrated, it has been impossible to fulfill criteria necessary to prove causality.

As discussed previously (Table I), a number of disorders are associated with mesangial IgA deposition and a subset of these diseases, e.g. celiac disease (42) and neoplasms (43,44), have the potential for continued

TABLE VII

FACTORS PRECIPITATING EPISODES OF GROSS HEMATURIA IN A POPULATION OF PATIENTS WITH IGA MESANGIAL NEPHROPATHY

	N	%
Number of patients (% of total population) with precipitating infectious events	51	56
Respiratory tract		70
Gastrointestical tract		26
Urogenital tract		4
Others		--
Number of patients (% of the total population) with strenuous physical effort as precipitating event	2	2

(From Ref. 41)

presentation of antigenic stimulus. Nonetheless, with respect to Berger's disease, there is no direct evidence that episodic antigenic stimulation of IgA production is critical to either the initiation or propagation of the process. Development of hematuria in association with infections in afflicted individuals may simply represent transient aggravations in the manifestation of an unrelated primary process through synergistic or additive pathogenetic effector mechanisms.

D. Immunologic Mechanisms

Potentially more accessible to investigation of mechanisms in pathogenesis are immune system derangements. Abnormal IgA, the complement system, and circulating immune complexes have all been implicated as playing a role in Berger's disease. As will be discussed, there is no unifying finding and most studies have been of a clinical nature and have therefore focused upon associations. Thus, it is often not clear whether any finding, if real, relates in a primary manner to disease development, or whether the observation is a

trivial epiphenomenon or simply an observation of a distal event in the effector limb of the process.

It has been observed that 50% of patients with Berger's disease have elevated serum IgA levels at the time of disease presentation (19,45). Shown in Figure 8 is a longitudinal study documenting the IgA levels in two subsets of patients with Berger's disease: those who present with elevated IgA levels and those who do not. The observation is clear that the levels of IgA tend to remain relatively constant in both settings (46). Definition of a causal mechanism from this appears unlikely, as both groups have a near identical

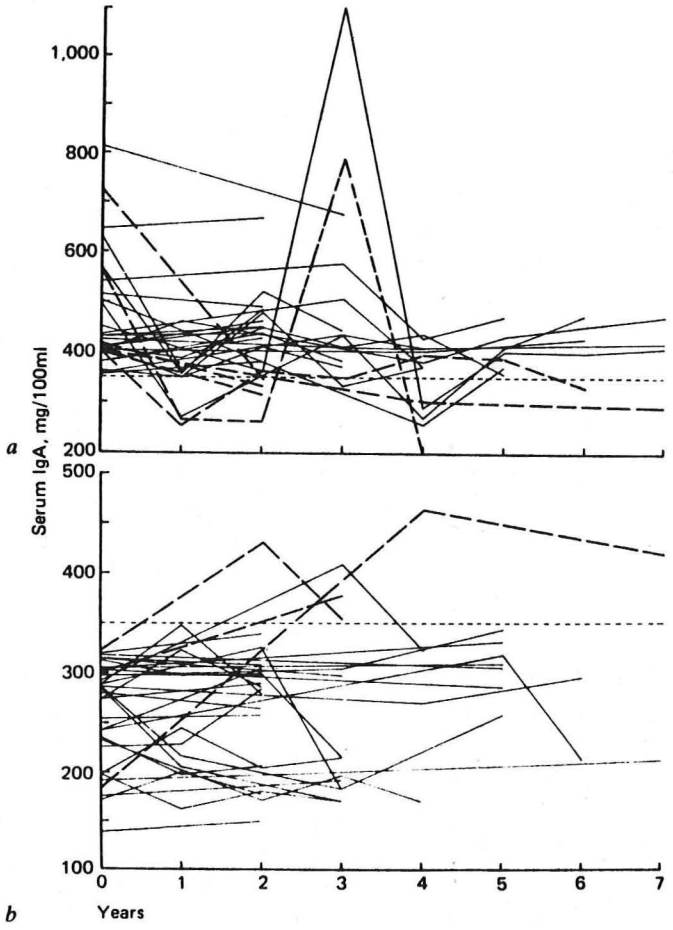


Figure 8: Serial serum IgA determinations in 66 patients with idiopathic IgA mesangial nephropathy. a Patients with abnormally high levels at first determination. b Patients with normal levels at first determination. From Ref. 46.

course and, indeed, one study has suggested that an elevated IgA level may be protective (47).

It has been observed that evaluation of serum IgA levels in these patients may be the exact opposite place where one should look for derangements in IgA per se; that is, the glomerulus with its sieving properties may have already screened from serum the critical factor(s) that provoke glomerular injury. In one study IgA was acid-eluted from biopsy specimens obtained from patients with IgA nephropathy (48,49). Shown in Figure 9 is the size distribution of IgA and IgA complexes obtained from such an eluate. As can be seen, there is a tendency toward deposition (or elution) of polymeric IgA. Similar studies were performed to determine the isoelectric point of the IgAs, and it has been found that the eluted IgA bears a greater anionic charge than IgA from sera (49). While this suggests that the polymerized form of IgA may be pathogenetic, no control eluates were performed, and the IgA eluted represented 0.1% of eluted protein, calling into question whether this finding might be an artifact due to poor recoveries.

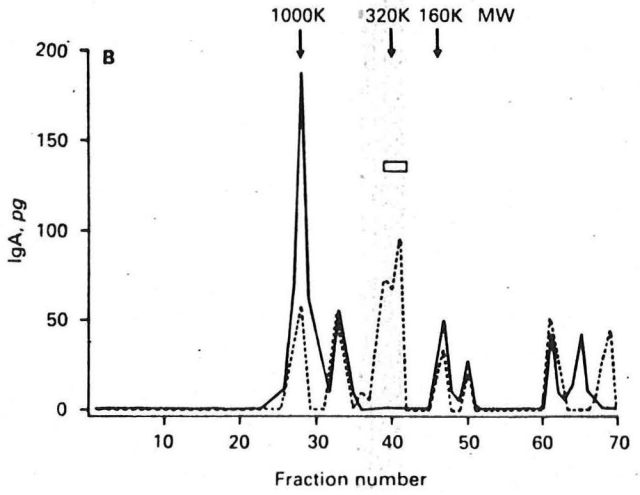


Figure 9. HPLC sizing of mesangial eluates from patients with IgA nephropathy. Solid line: HPLC performed at pH 6.8; dashed line: pH 3.5. From Ref. 48.

Circulating Immune Complexes

As has been reviewed in recent Grand Rounds presentations, the glomerulus, and specifically, the mesangium, is a frequent site of immune complex formation and deposition. This is due in part to the permselectivity of the glomerulus with respect to complex size and charge. In addition, the role of such deposition in the pathogenesis of a wide variety of glomerulonephritides has been well described (50,51). Accordingly, this discussion will focus on the potential role of immune complex deposition in the pathogenesis of IgA nephrology.

Circulating immune complexes, composed in part of IgA, have been demonstrated in some patients with IgA nephropathy (52-54). Shown in Figure 10 are the results of studies measuring levels of polymeric IgA, with or without secretory component, in normal subjects, and in patients with documented IgA nephropathy (55).

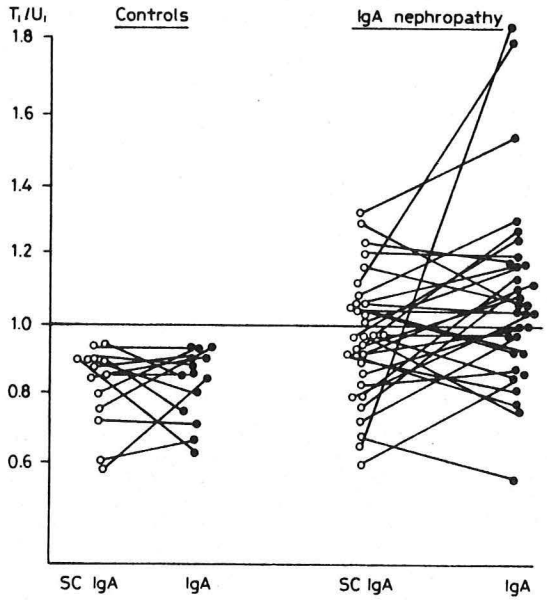


Figure 10: Presence of circulating immune complexes composed of polymeric IgA and polymeric IgA with SC in patients with IgA nephropathy. From Ref. 55.

As shown, there is a trend toward increased serum levels of both polymeric IgA, and polymeric IgA containing SC in patients with Berger's disease. This is underscored by the previously described study, in which acid eluates of biopsy specimens from patients with IgA nephropathy were shown to contain, in some instances, polymeric IgA (48).

Associations of disease activity with the presence of such complexes have been noted, of the type illustrated in Figure 11, where it is shown that in some patients, the presence of circulating immune complexes does appear to correlate with hematuria.

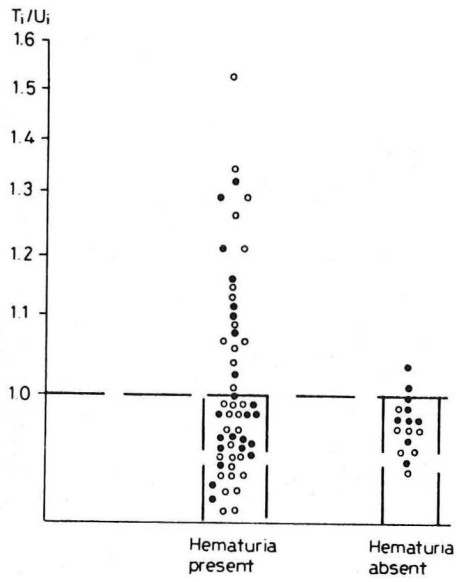


Figure 11: Correlation of the presence of circulating immune complexes with hematuria. From Ref. 55.

From such observations has sprung the speculation that in some instances complement activation may be provoked by the presence of such complexes (56). Supportive of this notion is the finding of a general correlation of the amount of C_3 within the mesangium and severity of the pathologic lesion (57).

Summary of Pathogenesis

What appears to be most lacking in our understanding of the pathogenesis of IgA nephropathy is the nature of the primary, predisposing host factor(s) responsible for initiation of the process. To my view, an indirect, HLA-mediated, tendency toward the development of Berger's disease seems unlikely. The presence of an undetected viral agent, although perhaps responsible for a disease subset, also appears not to be a unifying pathogenetic mechanism; transplantation of kidneys from individuals affected with Berger's disease into normal recipients would seem to be a likely infection transmission vehicle, yet in such instances, the observation is that of disease remission in the transplanted kidney (56,58).

Once the disease process is initiated, however, evidence is most supportive of the notion that glomerular injury occurs by means of polymeric IgA deposition with activation of complement through either the classical or alternate pathways. In addition, the possibility of multifactorial causes remains, and in this regard, the existence of a directly inherited glomerulopathy remains an active possibility.

Clinical Aspects

As noted in the introduction, the predominant clinical features of IgA nephropathy include microscopic or macroscopic hematuria, proteinuria and hypertension. Hematuria either by history or urinalysis is the most common finding leading to diagnosis (4). Shown in Table VII are the incidences of various forms of hematuria at presentation.

The age of presentation is highly variable, but the peak incidence is between ages 25-34 (41). That the disease occurs predominantly in males was noted earlier (4), and is also shown in Figure 12.

TABLE VII

PRESENTING SIGNS OF IGA NEPHROPATHY

Presenting Syndrome	N	%
Macroscopic hematuria	209	55.8
Recurrent	136	36.3
Isolated	70	18.7
"Nephritic"	3	0.8
Persistent microscopic hematuria without gross hematuria	165	44.2

(From Ref. 41)

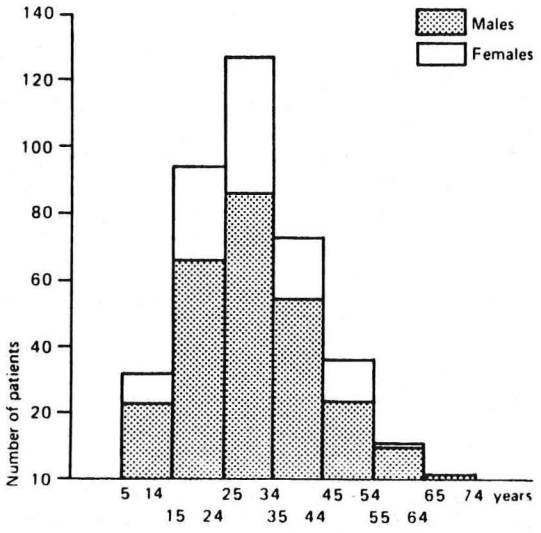


Figure 12: Age at clinical onset in 374 patients with idiopathic IgA mesangial nephropathy. (From Ref. 41.)

As noted in Table VII, infections, particularly respiratory or gastrointestinal, are not an infrequent precipitant of the hematuria. There is a common association of a decrease in GFR with macroscopic hematuria (59,60). In most instances, this is transient and GFR rises after resolution of the episode of hematuria.

Hypertension is also frequently present at the time of diagnosis (19), as shown in Figure 13.

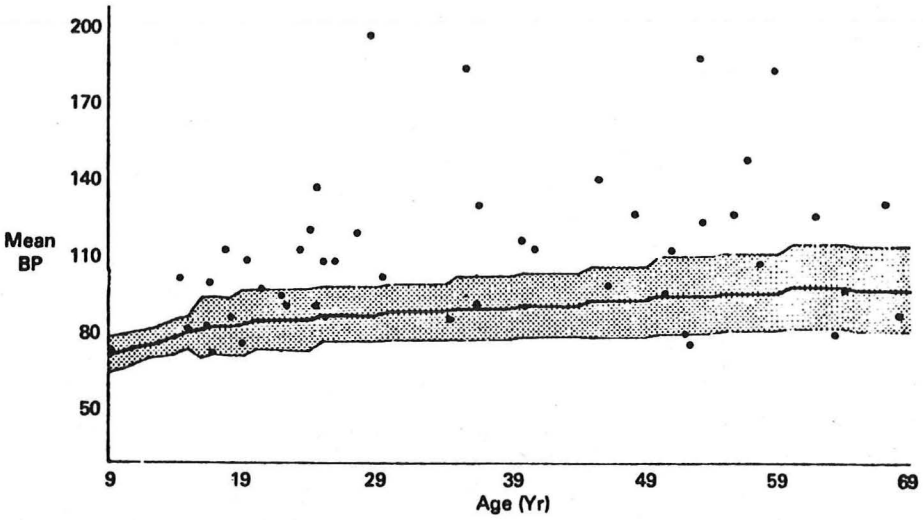


Fig. 13: Mean blood pressure is plotted against age of presentation and compared with normal mean blood pressure expected for age. (From Ref. 19)

The mean blood pressure is most commonly mildly to moderately elevated, and as will be discussed later, antihypertensive agents are the only indicated therapy in this disorder at present.

Although proteinuria is most commonly of a non-nephritic degree, episodes of severe proteinuria are clearly documented and this is felt to be correlated with a poor prognosis (61-63).

Lastly, IgA nephropathy can present with, or have during its course, a fulminant, rapidly progressive fall in GFR which is irreversible (63-65).

Diagnosis

As noted in the introduction, diagnosis of IgA is absolutely dependent upon a renal biopsy in order to demonstrate the presence of IgA by immunofluorescence. Arriving at the diagnosis is less a matter of clinical judgment than appropriate evaluation of hematuria. As is always the case with documented hematuria, evaluation should include cystoscopy and evaluation for a malignant source of red cells from the kidney through IVP, sonography and/or an abdominal CT scan. Should such an evaluation prove unrevealing, then a renal biopsy is the last step in evaluation.

Disease Course and Prognosis

Although somewhat misleading because of the tendency of episodes of hematuria to be associated with reversible declines in GFR (60), the finding of a lower creatinine clearance in patients presenting with IgA nephropathy (19) underscores the findings that this is not a benign disease. Shown in Figure 14 are creatinine clearances at the time of diagnosis of Berger's disease.

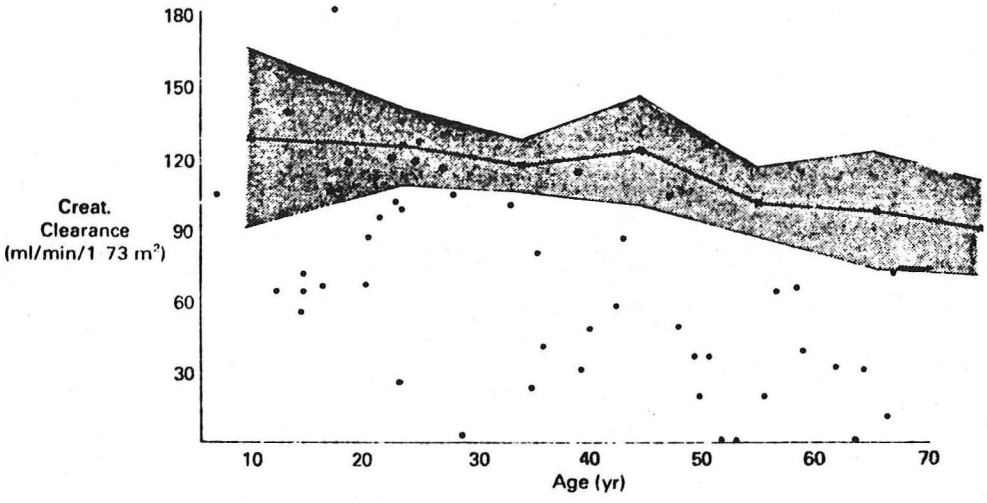


Fig. 14: Initial values for creatinine clearance plotted against age compared with the normal values. (From Ref. 19)

The actual incidence of the development of renal insufficiency and end-stage renal disease is still under evaluation, however, a representative acturarial renal survival rate is shown in Figure 15. Up to 30% of patients are shown to eventually develop end-stage renal disease (47), with a highly variable rate of progression (64). In some instances, renal failure develops within 3-4 years, whereas in other instances, the disease process consumes 25 years. As a positive note, the majority of patients with Berger's disease do not develop renal insufficiency of a degree which requires dialysis.

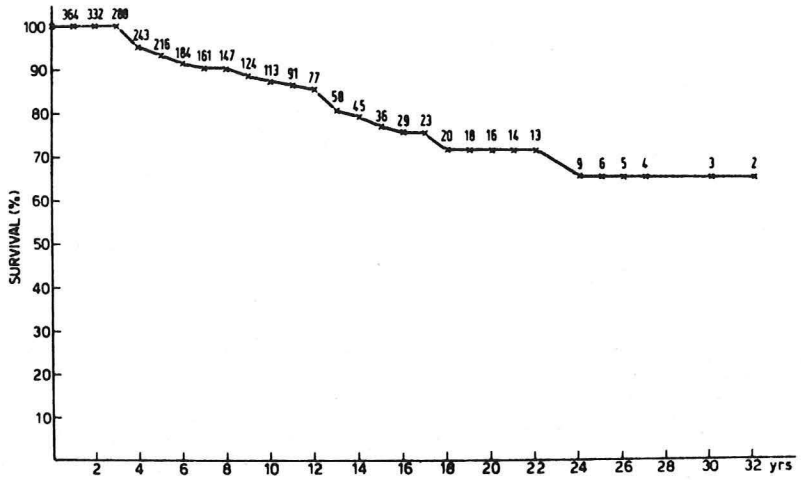


Fig. 15. Actuarial renal survival rate in 374 patients with IgA mesangial nephropathy. (From Ref. 47)

Considerable attention has been focused upon prognostic indicators in the progression of IgA nephropathy (67), and disease features which bode a poor outcome as shown in Table VIII.

Of these features, the first four [increased age of onset (20,68), persistent or heavy proteinuria (12,69), persistent hypertension (19), and severe biopsy findings (70,71)] are well correlated with poor outcome. As noted previously, a decreased GFR at presentation may be transient, in association with an episode of hematuria (60), and most studies include too few female patients to be certain of the role of gender in governing disease progression.

TABLE VIII

POOR PROGNOSTIC SIGNS IN IGA NEPHROPATHY

1. Increased age at onset
2. Hypertension
3. Severity of biopsy findings
4. Proteinuria
5. Male sex
6. Decreased GFR at presentation

[Modified from Silva (5)]

Therapeutic Approaches

At the present time, there is no agent which has been shown to alter the course of IgA nephropathy, although in certain instances, ongoing trials and unconfirmed studies suggest at least potential for amelioration. As pointed out previously, hypertension is frequently associated with Berger's disease (19) (likely as a secondary effect) and is the case with all glomerulopathies attended by elevated blood pressure, aggressive treatment is warranted.

The armamentarium in renal therapeutics is a short list and most agents (with the notable exception of cytotoxic agents and cyclosporine) have been given trials. Steroids administrated both by pulse during acute exacerbations in the course of disease and by chronic oral administration appear to be of no benefit, except in the small subset of patients who have frank nephrotic syndrome. In such instances, dramatic remissions in proteinuria have been induced (72). In an attempt to abrogate the putative antigenic stimulation resulting in IgA nephropathy, tetracycline has been tested in a controlled study and was shown to be of no benefit (73). Danazol has been tested in an attempt to "solubilize" mesangial IgA deposits. In a preliminary report (74), there appears to have been some decrease in proteinuria, but clearly further studies are indicated in that the initial study suffered from a limited number of patients (N=9).

More suggestive are trials with two other agents: Dilantin and eicosapentanoic acid (fish oil). With respect to the former, available evidence indicates that the drug may be of benefit in treatment of acute hemorrhagic episodes (75), although chronic studies indicate little benefit (76). With respect to eicosopentanoic acid, a single controlled study involving 20 patients indicates that this agent may prevent progression of IgA nephropathy (77). The mode of action is conjectural and further follow-up studies are required.

Thus, the mainstay of therapy in "management" of Berger's disease should, at present, be restricted to antihypertensive agents where indicated. An exception exists in patients with severe nephrotic syndrome, in which case, a course of steroids (oral prednisone) is warranted to determine if these patients belong to the small subset of steroid-responders.

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