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PERSPECTIVES IN CLINICAL NEPHROLOGY

IgA nephropathy

Since immunoglobulin A nephropathy (IgAN) was first described in the seminal papers by Berger [1, 2], we have learned much descriptively about its epidemiology, associations, natural history, and pathology, but the pathogenetic mechanisms remain largely uncertain. Although the histopathologic criterion for IgAN—the dominance or codominance of IgA deposition in the mesangium—suggests a single entity, it may as well characterize a group of diseases or "IgA-associated nephropathies," a concept that better suits this discussion. From the outset [2], Henoch-Schönlein purpura (HSP), clearly a systemic illness, has been closely linked to IgAN, which is defined by the absence of systemic features. Indeed, in some studies investigators include HSP as part of the spectrum of IgAN. This view is justified by several linkages between these two disease entities. Other considerations in the spectrum of glomerulopathies characterized by IgA deposition, such as nephritis associated with systemic lupus erythematosus (SLE) and hepatic glomerulosclerosis, are clinically distinct and will be mentioned only as they relate to the differential diagnosis.

The IgA system

The primary function of the IgA system is to prevent the invasion of the internal milieu by a vast array of microbial, food, and environmental antigens [3]. Familiarity with some basic features of IgA biology provides a helpful foundation for understanding the significance of some clinical and pathogenetic observations: More IgA is produced daily—about 66 mg/kg body weight—than all other immunoglobulin isotypes combined [4]. Two distinctive systems produce IgA: the systemic compartment, which includes the bone marrow, lymph nodes, tonsils, and spleen; and the mucosal or secretory system, which includes the gut, salivary glands, respiratory tract, and breast. These systems appear to function for the most part independently of each other [5]. In humans, two isotype subclasses, IgA1 and IgA2, are recognized along with two allotypes of the IgA2 subclass, A2m(1) and A2m(2). Since the A2m(1) allotype, unlike A2m(2), is not connected by interchain disulfide bonds, it is more readily cleaved by IgA bacterial proteases [6]. IgA2 is produced predominately in the mucosal compartment; its production in the systemic compartment is less than 10% of the total. In the systemic compartment, monomers predominate whereas multimers do in the secretory compartment. Multimeric IgA—as well as IgM—contains J-chain, a component that is linked to the heavy chain in the formation of multimers. Multimeric IgA also acquires secretory component at the basolateral membrane of epithelial cells; secretory component is necessary for the secretion of IgA across the mucosa [7].

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Epidemiology

IgAN is considered the most common glomerular disease worldwide [8]; its prevalence varies considerably among and within countries. In the western Pacific rim, particularly Japan, prevalences approaching 50% of all glomerular diseases have been observed [9] whereas in Europe, lower prevalences of 10 to 30% have been reported [10]. In the United States, while rates as low as 2% have been reported in some areas [10], American Indians in the Southwest have a remarkable prevalence of over 35% [11]. As emphasized by several authors [12, 13], it is now generally recognized that the local indications for kidney biopsy as well as health screening practices will profoundly influence these statistics. For example, in Great Britain, where early studies reported rates of less than 5% [14], a more recent careful analysis of kidney biopsies in Scotland showed that 37% of patients who had a biopsy for the diagnosis of asymptomatic hematuria had IgAN [15]. In addition, the prevalence of other diseases characterized by IgA mesangial deposition, particularly liver diseases, must be carefully excluded when a restricted group shows a high prevalence of apparent IgAN.

Gender and race are important factors in the epidemiology. Virtually all studies show a male predominance of at least 2:1 [12]. Unlike the high frequency of most other glomerular diseases in blacks, both IgAN and HSP are uncommon in blacks whether in the United States or in Africa [16, 17]. This finding is not related to the frequency of kidney biopsies among races. This low prevalence of IgAN in blacks has been postulated to be related to a structural property of IgA2, since the frequency of the A2m(1) allotype is 0.98 in whites but only 0.36 in blacks [18]. Because the A2m(2) allotype is resistant to cleavage unlike A2m(1), homozygosity for the A2m(2) allele in blacks was predicted to be protective against IgAN [19]. This hypothesis would predict that blacks with IgAN should have the A2m(1) allotype, which predominates in whites. However, in a study of 18 black patients with IgAN, only three were homozygous for A2m(1) while four were homozygous for A2m(2) and 11 were heterozygous [20]; the clinical course did not appear to differ among these three groups. The clinical course in blacks with IgAN also does not differ significantly from that in whites [21]. Thus, this structural difference between the two allotypes and the lower frequency of the A2m(1) allotype in blacks does not account for their low prevalence of IgAN.

Familial and regional clustering of IgAN has also been observed. After the initial report of a patient with IgAN with five family members who had hematuria and proteinuria [22], IgAN in identical twins was subsequently confirmed by kidney biopsy [23]. Since 1978, scattered reports of single families with IgAN [24] were followed by the study by Julian et al [25] of a pedigree encompassing seven generations; this included 14 patients with biopsy-proven IgAN, 17 with clinical hematuria or proteinuria, and 6 who had died of Bright's disease according to their death certificate. This pedigree that reaches back nearly 200 years

strongly suggests a genetic predisposition for at least some patients with IgAN. The true frequency of familial IgAN remains uncertain because no serologic marker is yet available and the diagnosis depends on the histopathology of the kidney. More recently, Schena, Scivittaro and Raineri studied 269 relatives from 48 families of IgAN patients and found urinary abnormalities in about 23% of the relatives [26]. In addition, a variety of abnormalities of IgA immunobiology were noted in these relatives including high serum IgA concentration, increased levels of IgA-IgG complexes, increased serum multimeric IgA and IgA rheumatoid factor, increased interleukin-2 and interleukin-4, and increased IgA1 production by peripheral blood mononuclear cells [26]. The significance of these findings will be discussed later.

Further support for the importance of genetically-determined factors has been sought in studies of HLA antigens. Initially, IgAN was associated with HLA Bw35 [27]; in subsequent studies from Japan, HLA DR4 was strongly associated [28]. Overall, reports of associations of HLA antigens or the lack thereof with IgAN have painted a confusing picture. Unfortunately, most of these studies have been in relatively small populations; they have been summarized by Berthoux et al [29]. In a recent study of 196 patients with end-stage renal disease (ESRD) due to IgAN, the odds ratios for B27 (2.02) and DR1 (1.79) were significantly increased and for DR2 (0.57) significantly decreased as opposed to those patients with ESRD due to focal segmental glomerulosclerosis in whom no association with any HLA antigen was found [30]. The etiology of ESRD in this study was obtained from the transplant nephrologist and not confirmed by review of biopsy reports; this is a minor detraction. Rather, the large number of patients, the comparison with focal glomerulosclerosis, and the severity of disease lend strength to the findings. Whether a heterogeneous nature of IgAN or geographic variation accounts for the differences among studies of HLA associations is problematic. At present, no positive or negative association of HLA antigens can be used for diagnostic purposes. The value of these associations for prognosis in this most recent study requires confirmation which should be forthcoming from other transplant populations which uniformly have the necessary HLA typing.

Clinical presentations

Typically, IgAN presents with painless macroscopic hematuria frequently at the time of infectious illnesses, which are most often pharyngitis or tonsillitis and less often pneumonia, gastroenteritis, or urinary tract infection [31]. The course is distinctively different from that of post-infectious glomerulonephritis in which the onset of macroscopic hematuria occurs 7 to 14 days after the infection. The episode is usually brief—about 24 hours—but may last for as long as a week. About 40 to 50% of patients present with macroscopic hematuria [12]. It is more common in children and decreases in frequency with age. Occasionally, flank or abdominal pain may be associated, and it can be severe. The finding of IgA vasculitis in the ileum of a patient with apparent IgAN and abdominal pain forges a clinical link between IgAN and HSP [32].

Microscopic hematuria usually with proteinuria constitutes the other common initial presentation in another 30 to 40% of patients. Macroscopic hematuria will occur at sometime in the course for about 20 to 25% of this subgroup. Obviously, urinary screening procedures, as are employed in Japan, will markedly increase the percentage of patients presenting with microscopic hematuria or chance proteinuria as well as the overall prevalence of IgAN.

Table 1. Diseases sporadically associated with mesangial IgA deposition

Connective tissue diseases
Ankylosing spondylitis, rheumatoid arthritis, mixed connective tissue disease, post-infectious arthritis
Intestinal
Celiac sprue, ulcerative colitis, regional enteritis
Dermatologic
Dermatitis herpetiformis, psoriasis
Neoplastic
Carcinomas (bronchogenic, laryngeal, mucin-secreting), IgA gammopathy, mycosis fungoides, non-Hodgkins lymphoma
Hematologic
Cyclical neutropenia, mixed cryoglobulinemia, immune thrombocytopenia, polycythemia
Miscellaneous
Idiopathic pulmonary hemosiderosis, sarcoidosis, retroperitoneal fibrosis, amyloidosis, myasthenia gravis, leprosy, HIV infection [38, 39], thin basement membrane nephropathy [148]

Acute renal failure with edema, hypertension, and oliguria occurs in less than 10% of patients [12]; 20–25% of this subgroup may require dialysis [31]. A small percentage of these latter patients have crescentic glomerulonephritis [33, 34]. As with most forms of glomerulonephritis, hypertension is common. It occurs infrequently at the time of initial presentation (5 to 10%), but more commonly as the course of the disease lengthens (30 to 40%) or when IgAN presents beyond the fourth decade of life.

Nephrotic syndrome is an uncommon presentation occurring in about 5% of all patients, but more frequently in children and adolescents [13]. It may occur in the setting of diffuse proliferative glomerulonephritis with or without sclerosis [35, 36]. Alternatively, the IgA deposition may occur with the diffuse epithelial cell foot process fusion characteristic of minimal change nephropathy.

IgAN has been associated with several diseases [37]. Most of these associations appear to be random with no hint of pathogenetic linkage (Table 1). However, the associations with celiac sprue (CS) and dermatitis herpetiformis (DH) are rather frequent. CS is caused by the gliadin fraction of gluten. It is characterized by diarrhea, malabsorption, lymphocytic infiltration of the lamina propria of the small intestine and circulating anti-gliadin antibodies; 10% of these patients have DH. On the other hand, DH is characterized by IgA deposition in the skin and usually asymptomatic gluten-sensitive enteropathy. CS and DH are clinically linked and IgA deposits in the mesangium may be part of their probable common pathogenesis. Alternatively, both CS and DH could be clinical manifestations of a disorder of IgA metabolism that more commonly presents as IgAN or HSP. Although the association with human immunodeficiency virus (HIV) infection [38, 39] is uncommon, it is of particular interest because of the presence of circulating idiotypic anti-immunoglobulin antibodies, which are also found in IgAN. Two other diseases in which mesangial IgA deposition occurs frequently are systemic lupus erythematosus (SLE) and hepatic cirrhosis; their histopathologies will be reviewed later. The clinical presentations and serology of SLE are sufficiently distinct that they should not be confused with IgAN or HSP.

Although HSP occurs most commonly in childhood, it has been reported as well in 70-year-old patients [40]. It is important to

recognize that, unlike IgAN which can be diagnosed only by kidney biopsy, HSP can be diagnosed by clinical criteria: abdominal pain, arthritis, and palpable purpura. Although renal manifestations are not essential for the diagnosis, one could speculate that mesangial IgA deposition may be universal in HSP. Where clinical criteria alone are used as evidence of nephritis in HSP, it is often assumed that mesangial IgA deposition is present. Thus, the prevalence of nephritis in HSP varies widely depending on the criteria used to make the diagnosis of renal involvement.

Diagnosis

Presently the diagnosis of IgAN can be made only by kidney biopsy. As suggested by the spectrum of clinical presentations, the light microscopic findings range from minor mesangial changes through focal and diffuse proliferation to crescentic glomerulonephritis [14, 41–43]. Again, this spectrum will be skewed toward more severe lesions because these are usually associated with a greater magnitude of proteinuria and lower glomerular filtration rates (GFR) which, in turn, are likely to prompt the clinician to perform a kidney biopsy.

The immunohistology is the crux of the diagnosis in which dominant or codominant mesangial deposition of IgA is the *sine qua non.* IgG and IgM are often present in a similar distribution. IgA only is present in about 15% of biopsy specimens [9, 14, 22, 44]. Variable degrees of capillary wall staining by IgA are seen in a small percentage of cases. Immunoglobulin λ light chain is found in excess of the κ isotype in the majority of cases of IgAN unlike in other glomerulonephridities [45]. Immunostaining for C3 and terminal complement components is nearly universally present while C1q and C4 depositions are absent or of low intensity. The histopathology of the kidney is identical in IgAN and HSP. Further evidence strengthening the linkage between these two diseases is that antibodies eluted from kidney biopsy specimens from patients with IgAN or HSP cross react with one another but not with kidney tissue from patients with other diseases [46].

In the differential diagnosis of mesangial IgA deposition, the immunohistology of lupus nephritis characteristically shows IgG, IgM, and IgA together. Lupus nephritis and not IgAN is likely if C1q is present at 2+ intensity or greater [44]. These immunohistological findings together with differences in the clinical presentation and serology readily distinguish lupus nephritis from IgAN or HSP. Hepatic glomerulosclerosis can usually be excluded on clinical grounds, but the presence of liver disease makes the diagnosis of IgAN *per se* more difficult. In this regard, IgA mesangial deposition is usually absent in patients with hepatic cirrhosis who have been biopsied for the diagnosis of clinically evident glomerular disease [47].

Tests of serum and urine are usually directed at two clinical questions: diagnosis and/or severity of the renal lesion. Unfortunately, in both IgAN and HSP, specific and sensitive tests for these purposes are not currently available. Serum total IgA concentration (this is what is routinely measured when serum IgA is requested from the clinical laboratory) is elevated in 33 to 50% of adults with IgAN and in a somewhat higher percentage in children [48]. Serial determinations have not been made or correlated with any measure of the severity or activity of the disease in any sizable population. Thus, this test is not worthwhile for either making the diagnosis or following the course of the disease. High concentrations of λ light chain are a distinctive feature of serum IgA in IgAN unlike the predominance of the κ isotype in normal serum [49]. The significance of this finding for pathogenesis is unknown. Urinary immunoglobulins are not distinctive in IgAN [50].

Although the presence of alternative complement pathway proteins in the glomerulus suggests activation of complement in the pathogenesis [42, 51], serum complement components and control proteins are normal in IgAN [52]. Nevertheless, several deficiencies of complement proteins have been associated with both IgAN and HSP [53]. These include complete C3 deficiency, partial H, P, I, C2, and C4BP deficiencies, and C4 isotype deficiency. The C3F and the BfF phenotypes also have been associated in two studies. While determinations of complement profiles may provide useful linkage information in familial IgAN, they do not help with either diagnosis or assessment of activity.

Determination of IgA-fibronectin aggregates initially showed promise of providing the clinician with a serologic test to diagnose IgAN [54, 55]. Unfortunately, further study has shown that, while strongly positive levels of these aggregates may help to differentiate IgAN from other forms of glomerulopathy, this test is not diagnostic [56]. In that study, only 25 of 52 patients had an elevated level of these aggregates on at least one occasion during the course of their disease. The sensitivity of the test is not sufficient to make the diagnosis, and the level does not correlate with the activity or severity of the glomerular lesion. Furthermore, the specificity of the test has recently been challenged [57]. Indeed, the binding of fibronectin may be a normal process enhanced by circulating IgA immune complexes [58, 59].

Anti-neutrophil cytoplasmic antibodies (ANCA) are distinctly uncommon in IgAN and HSP. A recent cross sectional and longitudinal study [60] showed IgG ANCA in only 2 of 100 patients with IgAN and in none of 30 patients with HSP; none of the 50 patients followed serially developed ANCA. No IgA ANCA was detected.

As will be discussed later, immunoregulation appears to be defective in IgAN. Most of the serum assays that provide evidence for such defect(s) are not routinely available and have been carried out mainly in the course of clinical research. However, levels of serum IgA rheumatoid factor (RF), which is an IgA antibody against the Fc portion of IgG, are increased in both IgAN and HSP [61–63]. Eight of 25 patients (32%) had elevated serum IgA RF levels; only one of these eight had a elevated IgM RF [62]. In addition, 13 of 24 children with HSP (54%) had elevated IgA RF, but none had elevated IgM or IgG RF [63]. Although these assays are not widely available and have low sensitivity for IgAN and HSP, contemporaneous determinations of IgA, IgG, and IgM RF have the potential of providing a serologic diagnosis of IgAN or HSP if a kidney biopsy was deemed inadvisable. Clearly, these tests would have to be applied in much larger numbers of patients before one could be confident of the specificity for IgAN. The presence of IgA RF in serum provides yet another link between IgAN and HSP.

Deposits of IgA in the blood vessels of the skin have been shown in IgAN and HSP [64]. However, IgA deposits do not occur with sufficient frequency in IgAN to recommend skin biopsy for diagnosis and occur frequently in other renal diseases [65]. Thus, both the sensitivity and specificity of this test is low.

Pathophysiology

An understanding of sequential events in the pathogenesis is the key to the development of successful therapy. Despite intensive investigation by several groups, a widely accepted hypothesis for the pathogenesis of IgAN has not yet emerged but several theories have their proponents. These theories have focused on at least four possibilities: (1) the ability of a certain antigen(s) to cross the mucosa or (2) a more generalized defect at the mucosal barrier *per se*; (3) an intrinsic defect in the structure of IgA; or (4) a defect in immune regulation, which includes the possibility of autoimmunity. Although the single diagnostic criterion of mesangial IgA deposition promotes a monolithic view of IgAN, this criterion may actually define a group of diseases. If that is the case, several different pathogenetic mechanisms may apply. However, at present only IgAN and HSP are clinically recognized entities. Since these two disorders share many of the same disease manifestations, it seems likely that they have the same pathogenesis. The following discussion will take this tack with notations of features common to both.

Animal models provide opportunities not available in patients to dissect pathogenesis. Early animal models of IgAN, which were produced by immunization with enteral or parenteral antigen [66] or by injection of preformed immune complexes [67], showed mesangial deposition of IgA and J chain indicative of multimers of immunoglobulins and the absence of secretory component. Unlike human disease, no third component of complement (C3) was present and no hematuria or proteinuria was shown. While these models provided insights into the nature of IgA deposited in the mesangium, they do not result in a kidney disease that reflects the human condition or produce the abnormal antibodies observed in patients with IgAN. More recent models including the ddY mouse [68] and the anti-Thy-1 rat [69] may relate more closely to human IgAN, but at this point the data are not yet sufficiently advanced to incorporate observations from these models into a review of the human disease.

The observations that pharyngitis, bronchitis, or gastroenteritis commonly precipitate an episode of hematuria in IgAN and the frequent association of IgAN with inflammatory bowel diseases (Table 1) suggest the first two of the above-mentioned pathogenetic possibilities [70]. An examination of the different characteristics of the products of the systemic and mucosal IgA systems provide some insight into these possibilities.

If the mucosa-associated system were the source of the increased macromolecular IgA in the circulation in IgAN, one would expect altered IgA production by that system in terms of the amount, size, or subclass, including some increase in serum IgA2 levels. Circulating IgA has been shown to contain increased levels of both total IgA1 and IgA1-containing immune complexes in patients with IgAN [62, 71, 72]. In bone marrow, IgA1-producing plasma cells are increased and produce predominantly multimers [73]. In contrast, both IgA1 and IgA2 production in saliva, a secretion of the mucosal system, does not differ in patients with IgAN compared to controls [74]. However, the same group of investigators showed that after immunization with tetanus toxoid, salivary IgA production increased in patients with IgAN but not in controls, suggesting that the mucosal system is abnormal in IgAN. However, serum IgA1 and IgA2 antibodies increased similarly in both groups [75]. Unfortunately, antibody size may not be a good differentiating feature for the system of origin because serum IgA antibodies specific to the immunogen are predominantly multimeric early in the immune response whether the route of immunization is enteral or parenteral [76]. Although these data are not in complete accord, on balance they favor a systemic origin for circulating multimeric IgA.

Specific exogenous antigens have been implicated by some studies. Oral ovalbumin loading in patients with IgAN shows some increase in specific multimeric IgA antibodies to this protein [77]. Conversely, antigen exclusion by a gluten-free diet decreases anti-gliadin IgA antibodies, IgA immune complexes, and proteinuria [78] in patients with IgAN. Increased serum levels of antibody against several microbes including pneumococcal polysaccharides, herpes simplex virus, cytomegalovirus, Epstein-Barr virus, and *E. coli* have also been reported. Some of these specific antibodies have also been detected in glomerular deposits [70]. The serum antibodies to a variety of common environmental antigens—both dietary and microbial—are almost exclusively multimeric IgA1. While these IgA1 antibodies are present in significant titers in serum, median values did not differ between normal humans and those with IgAN or HSP [79]. In addition, IgA2 antibodies were present in low titers and again did not differ between patients with IgAN and normal subjects [79]. The characteristics of serum IgA in these studies resemble those of IgA originating in the bone marrow-associated compartment more than those of the mucosa-associated compartment. Thus, the data suggest that the formation of IgA antibodies directed at a wide spectrum of environmental antigens is a normal event. In fact, increased serum IgA1 antibodies to several environmental antigens have been detected also in membranous nephropathy, minimal change disease, and membranoproliferative glomerulonephritis [80]. This reinforces the notion that IgA produced by the mucosa-associated system does not play a key role in the pathogenesis of IgAN. These data do not exclude a defect in the mucosal barrier in CS. However, if this were the case in IgAN and the antigens that gained access to the systemic IgA compartment evoked an abnormal antibody response, increased levels or abnormal forms of serum antibodies to environmental antigens would be expected in patients with IgAN. The data do not support such a mechanism.

The immunopathology of IgAN also provides important clues regarding pathogenesis. IgA may deposit in the mesangium because: (1) one or more of its physicochemical properties cause it to be trapped there; (2) it binds to a deposited antigen(s); or (3) it binds to an intrinsic mesangial antigen. Initial studies of IgA subclasses reported the deposition of both IgA1 and IgA2 in IgA-associated nephropathies [81] leading those authors to postulate that the mucosa played a pivotal pathogenetic role. However, Conley, Cooper and Michael [82] showed by using more specific reagents that IgA1 subclass selectively was deposited in the mesangium in IgAN, HSP and SLE. This nearly exclusive deposition of IgA1 has been confirmed by several investigators [79, 83–85], and is more consistent with IgA originating in the systemic and not the mucosal system. In hepatic cirrhosis, IgA deposits, if they occur, are usually IgA1 and IgA2, unlike those in IgAN or HSP. This suggests a different pathogenesis in hepatic glomerulosclerosis probably involving impaired biliary excretion of IgA multimers.

Other structural characteristics have been examined to determine the nature and origin of deposited IgA. The multimeric nature of deposited IgA antibodies has been suggested by the presence of J-chain in several studies [86–88]. However, because

IgM also contains J-chain, codeposits of IgM must be carefully excluded to conclude that multimeric IgA is present. Secretory component was seen commonly in hepatic glomerulosclerosis and SLE but rarely in IgAN and HSP [84]. Others have not observed secretory component in any IgA-associated glomerular disease [85]. Finally, IgA actually eluted from the kidneys of patients with IgAN has been characterized as multimeric with an anionic charge (pI = 4.5 to 6.8) [89]. Thus, these data suggest that deposited IgA is multimeric but they do not conclusively establish the IgA system of origin.

Antibodies to several viruses including herpes simplex, hepatitis B, adenovirus, and cytomegalovirus and to several foods including soy, bovine milk and rice proteins have been detected in the mesangium of patients with IgAN usually but not always coincident with IgA1 deposits [90]. Where tested, these antibodies are of the IgA1 subclass [79]. These studies must be interpreted with caution because the reactivity of some antisera, particularly polyclonal antibodies, may be non-specific with human tissue or other unrelated antigens. Nevertheless, the data show that no specific or characteristic microbial or food antigen has been identified in the glomeruli of patients with IgAN. Since similar circulating antibodies specific to environmental antigens are present in normal subjects as well as in patients with IgAN, it seems likely that the array of deposited antibodies has little or nothing to do with the nature of the particular antigens.

The physical and immunological characteristics of circulating, secreted, and deposited IgA join with several other lines of evidence to suggest that disordered immune regulation or production underlies the pathogenesis of IgAN and HSP. Among the IgA1-containing immune complexes, multimeric IgA1 RF has been shown in both IgAN and HSP. Increased IgG antibodies and decreased IgM antibodies against the Fab fragment of the α heavy chain have also been demonstrated in these patients [91]. Although a similar pattern of antibodies against immunoglobulins are also seen in patients infected with HIV [92], IgA deposition in the kidney is distinctly uncommon in HIV-infected patients [93], notwithstanding recent reports [38, 39]. This suggests that the mere presence of these circulating autoantibodies alone does not account for mesangial IgA deposition.

Further support for a more generalized disorder of immune regulation is the finding of two IgG antibodies to autoantigens present in the mesangium [94]. These antibodies were detected in sera of patients with both IgAN and HSP and the titer correlated with hematuria and proteinuria. Circulating anti-endothelial cell antibodies have been detected in IgAN, but are found in lupus nephritis and systemic vasculitis as well [95]. These data extend the spectrum of antibodies formed in IgAN to both fixed and circulating endogenous antigens.

The role of the complement in the pathogenesis is problematic. IgA is not a predictable or potent activator of complement but alternative pathway components nearly always accompany IgA deposits [96]. Although IgA immune complexes can activate the alternative pathway, they bind complement and C3b poorly. Since C3b is the natural ligand for the complement receptor, CR1, on human erythrocytes, IgA immune complexes may be more pathogenic for the kidney because of greater difficulty in safely clearing them from the circulation [97]. It has been postulated that IgG-IgA complexes are necessary for complement activation which may occur locally in the kidney and account for the presence of the membrane attack complex in the mesangium. However, mesangial C3 is present even in the absence of IgG or IgM deposits. Whether the amount of mesangial deposition of IgG or IgM might fluctuate during the course of disease to account for their absence in some instances is not known.

Abnormalities in the activity of the cellular immune system have been detected in IgAN and HSP. Studies of T lymphocytes suggest that increased T helper (CD4) lymphocytes and decreased T suppressor (CD8) lymphocytes occur with exacerbation of disease [98]. Specifically, Tα4 cells with the capacity to switch from IgM to IgA synthesis are increased in IgAN [99]. In response to tetanus toxoid, patients with IgAN more commonly had undetectable amounts of an IgG subclass (IgG1 and/or IgG4, and less commonly IgG3) while IgA concentrations rose [100]. These authors suggested that IgG to IgA switching was impaired in IgAN. In further support of a role for Tα4 cells, restriction fragment length polymorphism analysis in patients with IgAN has shown an increased frequency of the Sα1 allele, that portion of the gene that mediates the switch from IgM to IgA [101]. Transforming growth factor β, which induces the IgA isotype switch, and IL-5, which promotes differentiation in IgA-bearing B lymphocytes, may also be elevated in patients with IgAN [45]. Finally, increased production of IL-4, which may mediate the switch to IgA production, has been observed in patients with IgAN and their relatives [26].

Whether the number of circulating IgA-bearing B lymphocytes is abnormal in IgAN is controversial. The inconsistent results among several studies may relate to admixed T and B lymphocytes in the peripheral blood sample or may be dependent upon the activity of the disease at the time of sampling [102]. The use of mitogen stimulation also confounds the interpretation of some studies—not all cited here [45]. Nevertheless, a preponderance of *in vitro* studies shows increased production of IgA, IgG and/or IgM by B lymphocytes—even when clearly isolated from T lymphocytes—in patients with IgAN and HSP and their relatives [103–106]. Taken together, the data suggest that both T and B lymphocytes are engaged in supporting increased IgA production. However, excess production alone is an unlikely sole cause of mesangial IgA since IgA myeloma rarely results in tissue deposition. Thus, a structural—immunological or physicochemical—abnormality in the IgA produced by patients with IgAN has been sought as a possible cause of mesangial IgA deposition.

Polyclonal idiotypic antibodies directed against bovine serum albumin (BSA) have been shown in the sera and mesangiums of patients with IgAN, the titer of which correlated with hematuria [107]; a defect in anti-idiotype production was not shown. The fact that the idiotype was derived from serum IgG antibodies preselected for activity against BSA makes the significance of this observation uncertain [108]. To search for idiotypic antibodies that are pathogenic in IgAN, van den Wall Bake and coworkers took advantage of an opportunity to elute IgA from the renal cortex and isolated glomeruli of a kidney obtained from a patient with IgAN. Monoclonal anti-idiotypic antibodies specifically directed against those eluted antibodies were then developed [109]. Only five different monoclonal antibodies were raised; all reacted specifically against Vκ3a light chain and not toward any heavy chain. These antibodies reacted against pooled serum and plasma cells of patients with IgAN and normal subjects. In addition, they reacted against 26 of 31 kidney biopsies of patients with IgAN, 6 of 6 with HSP and virtually all kidney biopsies from patients with

lupus nephritis, membranous glomerulopathy, membranoproliferative glomerulonephritis, and essential mixed cryoglobulinemia. Thus, the only idiotype expressed in deposited IgA antibodies is shared not only by patients with IgAN but also a broad spectrum of glomerulopathies. This lack of specificity for IgAN may be due to a failure to identify a particular antigen in this case. Alternatively, it suggests that mesangial IgA is highly polyclonal. If the latter possibility is correct, the data would be consistent with the hypothesis that deposition is linked to some abnormal property of the polyclonal IgA antibody in IgAN.

Abnormalities in the structure of IgA in IgAN have not been intensively investigated thus far. Human IgA1 contains an unusual O-galactosylation hinge region on the heavy chain, a process that is under the control of the enzyme, β1,3-galactosyltransferase (β1,3-GT). The asialoglycoprotein receptor (ASGP-R) in the liver, which is the major site for the catabolism of IgA [110], has been shown to be specific for these terminal galactose residues. It is possible that decreased galactosylation or inaccessible galactose residues may alter the clearance of IgA1 or IgA1-containing immune complexes leading to mesangial deposition. In this regard, Mestecky et al showed that IgA1 in patients with IgAN is deficient in galactose residues [111]. They hypothesized that a deficiency of β1,3-GT may be an important primary cause of IgA deposition. A linkage between this structural abnormality and the evidence for polyclonal B lymphocyte activation will have to be incorporated into a coherent hypothesis. Conceivably, a structurally abnormal antibody is somehow not recognized in the feedback mechanism of antibody production thereby resulting in augmentated production. There is no evidence that elevated anti-α-galactosyl IgG antibodies in patients with IgAN and HSP during episodes of hematuria [112] is linked to defective galactosylation. These antibodies may be simply one of many circulating antibodies in IgAN.

Infrequently, serial kidney biopsies in patients with hematuria and proteinuria have uncovered patients with IgAN who did not show mesangial IgA deposition at the outset of their renal disease [113]. These cases challenge the notion that the IgA deposits lead to hematuria and proteinuria and the pathogenetic significance of these deposits. Early antigen deposition with or without cell-mediated immune responses, the rate of IgA immune complex formation and more effective clearance by mesangial cells that possess IgA Fc receptors or clearance by neutrophils which also have IgA Fc receptors are among the mechanisms speculated to explain these observations, which will have to be incorporated into any hypothesis regarding pathogenesis.

Although considerable data have been amassed on the role of cytokines, autocoids and growth factors in the pathogenesis of mesangial proliferation and sclerosis, their actions have not been shown to apply exclusively or largely to IgAN or HSP. These data will not be considered here even though therapeutic regimens of the near future may be directed at these pathways.

Prognosis

Chronic renal failure and ESRD is the eventual outcome in 30 to 35% of patients with IgAN. For example, of the 119 patients originally diagnosed at the Necker Hospital prior to 1973, 74 have had regular follow-up there. Of these, 22 are in clinical remission, 28 have chronic renal failure, and the remainder have persistent proteinuria or hematuria [114]. Life-table analysis of several series from Asia, Australia, Europe and North America shows a 10-year renal survival of 80 to 90% [115].

From the clinical standpoint, the important risk factors at the time of diagnosis for subsequent severe renal failure are renal insufficiency and proteinuria (>1.5 g/24 hr). Many investigators find that hypertension or the *absence* of macroscopic hematuria also predicts a poor outcome [115].

From the histopathologic perspective, glomerular sclerosis, interstitial fibrosis, and involvement of the glomerular capillary wall all bode a poor outcome [115]. Histologic remission of IgA deposits is uncommon [113].

Other factors have been associated with a poor outcome: IgAN is more severe in patients with C4A deficiency [116]. Increased frequency of HLA B-35 [117], B27, and DR1 [30] has been detected in patients with ESRD due to IgAN.

Treatment

Therapeutic trials that convincingly show a long-term beneficial effect on the progression of renal insufficiency in IgAN and HSP are wanting [118, 119]. Such trials are difficult to carry out because IgAN progresses toward renal failure slowly over several years in a minority of patients. No cure is known at present.

As with many glomerulopathies, corticosteroids with or without immunosuppresive agents have been used in several studies usually confined to patients considered to be at risk for progressive renal failure. Short-term trials in patients with heavy proteinuria have shown inconsistent results: Although Lai et al [120] found no benefit over four months, Kobayashi and coworkers observed stable renal function in patients with initial creatinine clearances greater than 70 ml/min treated with daily prednisone for over 18 months compared to those who received non-steroidal anti-inflammatory agents or anticoagulants [121]. More recently, a beneficial effect of alternate-day steroid therapy has been shown in a small uncontrolled trial over 54 months in six children with IgAN associated with more than 1 g/day of proteinuria or glomerular or interstitial sclerosis on kidney biopsy [122]. Based on these encouraging findings, Julian et al have been conducting a multicenter prospective trial of alternate-day prednisone compared to no treatment in patients with IgAN who are at risk by virtue of severe proteinuria (greater than 2 g/day) or biopsy evidence of chronicity [123, 124]. Prednisone was given thrice weekly, started at 60 mg/day, and tapered slowly to 10 mg/day by protocol over 24 months. The alternate-day regimen was used to minimize the often serious side effects of corticosteroid therapy. Only 11 patients have completed the protocol thus far [124] and no further deterioration in GFR has been detected in either group. Glucose intolerance developed in 2 of 17 treated patients. At this juncture, prednisone does not appear to offer a beneficial effect other than modest amelioration of proteinuria. Because of the indolent course, more patients and/or longer periods of observation will be necessary to reach a conclusion. A meta-analysis of randomized controlled trials of corticosteroids and/or cytotoxic agents supports the conclusion that corticosteroids reduce severe proteinuria (greater than 3 g/day) in patients with IgAN [125].

The exception to this uncertain effect of corticosteroids is found in children with IgA deposition in the setting of minimal change nephrotic syndrome, which shows classical diffuse epithelial cell foot process fusion. Such patients respond to corticosteroid

therapy with prompt resolution of proteinuria in keeping with the experience with typical minimal change disease [126, 127].

Combination therapy with cyclophosphamide, dipyridamole and warfarin has been used in two long-term trials. The primary benefit in both trials was a reduction in the magnitude of the proteinuria; no conclusive effect on GFR was observed [128–130]. Cyclosporin for 12 weeks decreased proteinuria but also creatinine clearance in treated patients [131]; no further studies on this agent have been reported.

Several other treatment regimens including phenytoin, anti-platelet drugs, eicosopentaenoic acid, urokinase, dapsone, sodium cromoglycate, dietary gluten restriction and plasma exchange have been tabulated and summarized by Clarkson et al [119]. With the exception of urokinase, none of these has been shown to be beneficial to preserve GFR. Urokinase therapy was compared to a variety of anti-platelet drugs in the control group without randomization. The rationale for this therapy was based on the finding of fibrinogen in the glomeruli of patients with IgAN [132]. Although it was concluded that urokinase improved GFR, this conclusion was based on a marked rate of rise of serum creatinine concentration in one patient in the control group who had proteinuria of more than 1 g/day. Urokinase cannot be recommended based on this study, regardless of the statistical conclusion.

The tonsils as a part of the systemic IgA system contribute predominantly IgA1 and may act as activators or effectors of IgA dysregulation in IgAN [133]. Tonsillectomy, which has not been vigorously pursued for its potential benefit, has recently been shown to be associated with a decrease in proteinuria (from 3.5 to 0.9 g/day after 4 years), hematuria and serum total IgA concentration in 34 patients with IgAN and recurrent infections. Whether all 34 patients were followed for at least four years is not stated [133]. The serum creatinine concentrations recorded in this report are difficult to interpret but did not appear to rise over the four years of follow-up. Since this magnitude of proteinuria is a poor prognostic sign (most all studies concur on this point), tonsillectomy clearly benefited these patients and did not adversely affect GFR. Thus, tonsillectomy appears to be indicated in patients with recurrent infection; whether other patients with IgAN would benefit is a question of some import that merits further careful study.

Deficiencies of essential fatty acids have been detected in patients with IgAN [134]. These patients, all 15 of whom were at increased risk for progressive renal failure by virtue of decreased GFR, heavy proteinuria or hypertension, were treated with fish oil supplements for one year at which time a significant decrease in proteinuria and increase in GFR were observed. Whether this beneficial effect of fish oil is on glomerulonephritis in general or is related specifically to IgAN cannot be determined from this study. A larger randomized clinical trial has been completed (**Note added in proof**).

Abnormalities of generalized immunoglobulin production—confined to not only IgA—have been recognized [92, 135]. Based on these data and the finding of a deficiency of mainly IgG1 subclass in patients with IgAN and HSP, a recent trial of high-dose immunoglobulin therapy proved successful in 11 patients with severe IgAN or HSP [136]. When intravenous followed by intramuscular immunoglobulins were administered over nine months, the decline of nearly 4.0 ml/min/month in GFR was nearly completely arrested along with a decline in hematuria and proteinuria over a median 14 month follow-up. Relapse appeared to be prompt if therapy was discontinued. Thus, administration of pooled human immunoglobulins appears to arrest the disease. Prospective, controlled trials are in order probably limited to patients at high risk for progression.

Hypertension and heavy proteinuria both are associated with a poor prognosis in virtually every study of the natural history of IgAN and HSP. Converting enzyme inhibitors (CEI) have proven superior to other antihypertensive agents in delaying the progression of renal failure and diminishing proteinuria. This has been shown for 22 patients followed for 20 months treated with CEI compared to 34 patients treated with β-adrenergic antagonists followed for more than 36 months [137]. In addition, a retrospective analysis of 115 patients with IgAN and more than 1 g/day of proteinuria showed that those who were hypertensive and treated with a converting enzyme inhibitor (CEI) had a slower rate of progression of renal insufficiency [creatinine clearance: (−) 0.4 vs (−) 1.0 ml/min/month] and a higher frequency of remission of proteinuria (18.5 vs. 1.8%) than those treated with other antihypertensive medications [138]. Therefore, treatment of hypertension in severe IgAN with CEI is superior to other antihypertensive regimens. Whether treatment with CEI is useful in normotensive proteinuric patients with IgAN is not known.

While some have lamented that we have not progressed beyond corticosteroid therapy in 25 years of study, others see brighter prospects for the treatment of glomerular disease [139, 140]. Several of the aforementioned treatments for patients at risk are new and must await support by further study before an unqualified endorsement is in order. Given that proviso, if a patient has rapidly deteriorating renal function (GFR > -2 ml/min/month), immunoglobulin therapy should be considered; hypertension should be treated with a CEI preferably; and, if only proteinuria (>1 g/day) is present, a course of alternate day corticosteroids may prove beneficial. As the new avenues of investigation in IgAN define specific steps in its pathogenesis, modern molecular biological agents can and are being developed. With new monoclonal agents capable of blocking the action of specific cytokines and growth factors, it may become possible to arrest or retard the progression of mesangial proliferation and sclerosis in IgAN and HSP as well as other forms of glomerulonephritis. However, as Couser has observed, we must overcome the organizational barriers for the prompt and effective assessment of such new agents for these diseases that are of relatively low incidence in the general population. He has called for the development of a single data bank—a national registry—for glomerulonephritis to provide the necessary pool from which studies with sufficient numbers of patients enrolled can obtain prompt answers [140]. Clearly, with the widespread availability of facsimile machines and computers, the involvement of the private nephrologist along with the academician with a minimum of effort is entirely feasible. Except for isolated efforts, the nephrology and nephropathology community in the United States is well behind our colleagues in other disciplines and countries in this regard. Now is the time to correct the problem.

Kidney transplantation in IgAN is effective and has also provided insights into some of its fundamental pathogenetic aspects. Mesangial IgA deposition has been shown to occur soon after transplantation [141, 142]. A patient with ESRD due to HSP also has developed mesangial IgA deposition in the renal allograft with no systemic manifestations [143], further linking HSP with IgAN.

On the other hand, when a kidney from a donor with subclinical IgAN was inadvertently transplanted into a recipient with ESRD due to a disease other than IgAN or HSP, mesangial IgA deposition promptly resolved [144]. These two observations strongly support the systemic nature of IgAN. The recurrence of mesangial IgA is not necessarily associated with recurrent progressive renal insufficiency. However, after several years renal failure due to IgA disease alone may ensue despite maintenance immunosuppressive drugs including cyclosporin [145].

Of all the common diseases that lead to ESRD, the cadaveric kidney allograft survival is highest in IgAN at both one-year (87%) and three-years (77%) [146]. Furthermore, Lim et al have recently observed that patients with IgAN who had IgA antibodies to HLA antigens had a 100% two-year kidney allograft survival compared to a 70% survival rate in IgAN patients who did not have antibodies against HLA [147]. They hypothesized that these autoantibodies to HLA antigens block IgG antibodies or inhibit cellular immune responses to enhance graft survival. Whatever the explanation, early kidney allograft survival is excellent in IgAN.

Summary

IgAN is the most common type of glomerulonephritis worldwide, and is found more in men and distinctly less in blacks. It presents with macroscopic hematuria in about 40 to 45% of patients, with microscopic hematuria and proteinuria in about 35 to 40%, and with nephrotic syndrome or acute renal failure in the remainder. The diagnosis continues to rely on the finding of the dominant or codominant mesangial deposition of IgA on immunohistologic examination of the kidney. No blood or urine test is sufficiently reliable for diagnosis. While the pathogenesis remains unknown, accumulating evidence suggests that polyclonal stimulation of immunoglobulins perhaps coupled with structural abnormalities of IgA play pivotal roles. These defects may account for the variety of autoantibodies detected in patients with both IgAN and HSP. While IgAN has an indolent course, about 30% of patients will reach ESRD after 20 years, particularly in those who present with hypertension, heavy proteinuria or renal insufficiency. At present, therapy is disappointing, but immunoglobulin supplementation and newer agents that interrupt the pathways of mesangial proliferation and sclerosis hold promise for the future. Kidney transplantation has shown excellent allograft survival.

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Note added in proof

A placebo-controlled, randomized trial has recently shown a decrease in the rate of rise in serum creatinine and in ESRD. DONADIO JV JR, BERGSTROM EJ, OFFORD KP, SPENCER DC, HOLLEY KE, for the Mayo Nephrology Collaborative Group: A controlled trial of fish oil in IgA nephropathy. *N Engl J Med* 331:1194–1199, 1994

References

1. BERGER J, HINGLAIS N: Les depots intercapillaires d'IgA-IgG. *J Urol Nephrol* 74:694–695, 1968
2. BERGER J: IgA glomerular deposits in renal disease. *Transplant Proc* 1:939–944, 1969
3. MESTECKY J: The common mucosal immune system and current strategies for induction of immune responses in external secretions. *J Clin Immunol* 7:265–276, 1987
4. MESTECKY J: Immunobiology of IgA. *Am J Kidney Dis* 12:378–383, 1988
5. MESTECKY J, RUSSELL MW, JACKSON S, BROWN TA: The human IgA system: a reassessment. *Clin Immunol Immunopathol* 40:105–114, 1986
6. KILIAN M: Degradation of immunoglobulins A1, A2 and G by suspected principal peridontal pathogens. *Infect Immun* 34:757–765, 1981
7. LAMM M: The IgA mucosal immune system. *Am J Kidney Dis* 12:384–387, 1988
8. JULIAN BA, WALDO FB, RIFAI A, MESTECKY J: IgA nephropathy, the most common glomerulonephritis worldwide. A neglected disease in the United States? *Am J Med* 84:129–132, 1988
9. UEDA Y, SAKAI O, YAMAGATA M, KITAJIMA T, KAWAMURA K: IgA glomerulonephritis in Japan. *Contrib Nephrol* 4:36–47, 1977
10. LEVY M, BERGER J: Worldwide perspective of IgA nephropathy. *Am J Kid Dis* 12:340–347, 1988
11. MELEG-SMITH S, TUNG KSK: Incidence of IgA-related nephritidies in American Indians in New Mexico. *Hum Pathol* 16:181–184, 1985
12. SCHENA FP: A retrospective analysis of the natural history of primary IgA nephropathy worldwide. *Am J Med* 89:209–215, 1990
13. HOGG RJ: Usual and unusual presentations of IgA nephropathy in children. *Contrib Nephrol* 104:14–23, 1993
14. SISSONS JGP, WOODROW DF, CURTIS JR, EVANS DJ, GOWER PE, SLOPER JG, PETERS DK: Isolated glomerulonephritis with mesangial IgA deposits. *Brit Med J* 3:611–614, 1975
15. PROPPER DJ, POWER DA, SIMPSON JG, EDWARD N, CATTO GRD: The incidence, mode of presentation, and prognosis of IgA nephropathy in Northeast Scotland. *Semin Nephrol* 7:363–366, 1987
16. GALLA JH, KOHAUT EC, ALEXANDER RC, MESTECKY J: Racial differences in the prevalence of IgA-associated nephropathies. *Lancet* 2:522, 1985
17. JENNETTE JC, WALL SD, WILKMAN AS: Low incidence of IgA nephropathy in blacks. *Kidney Int* 28:944–950, 1985
18. WANG AC, FUDENBURG HH: Genetics and evolution of human immunoglobulin A. *Adv Exp Med Biol* 45:161–165, 1974
19. NEELAKANTAPPA K, GALLO GR, BALDWIN DS: Immunoglobulin A nephropathy in blacks and homozygosity for the genetic marker A2m. *Ann Int Med* 104:287, 1986
20. CROWLEY-NOWICK PA, JULIAN BA, WYATT RJ, GALLA JH, WALL BM, WARNOCK DG, MESTECKY J, JACKSON S: IgA nephropathy in blacks: Studies of IgA2 allotypes and clinical course. *Kidney Int* 39:1218–1224, 1991
21. JULIAN BA, WYATT RJ, WALDO FB, KOOPMAN WJ, JACKSON S, SCHROHENLOHER RE, GALLA JH, MESTECKY J, CZERKINSKY C: Immunological studies of IgA nephropathy: Familial and racial aspects, in *Recent Advances in Mucosal Immunology,* edited by MCGHEE JR, MESTECKY J, OGRA PL, BIENENSTOCK J, New York, Plenum Publishing Corp., 1987, pp 1489–1498
22. DEWERRA P, MOREL-MAROGER L, LEROUX-ROBERT C, RICHET G: Glomerulites a depots d'IgA diffus dans le mesangium. Etude de 96 cas chez l'adulte. *Schweiz Med Wochenschr* 103:761–768 and 797–803, 1973
23. TOLKOFF-RUBIN N, COSIMI AB, FULLER T, RUBIN RH, COLVIN RB: IgA nephropathy in HLA-identical siblings. *Transplantation* 26:430–433, 1978
24. EGIDO J, JULIAN BA, WYATT RJ: Genetic factors in primary IgA nephropathy. *Nephrol Dial Transplant* 2:134–142, 1987
25. JULIAN BA, QUIGGINS PA, THOMPSON JS, WOODFORD SY, GLEASON K, WYATT RJ: Familial IgA nephropathy. Evidence for an inherited mechanism of disease. *N Engl J Med* 312:202–208, 1985
26. SCHENA FP, SCIVITTARO V, RANIERI E: IgA nephropathy: Pros and cons for a familial disease. *Contrib Nephrol* 104:36–45, 1993
27. MACDONAL IM, DUMBLE LJ, KINCAID-SMITH P: HLA and glomerulonephritis, in *HLA and Disease,* Paris, INSERM, 1976, p 203
28. HIKI Y, KOBAYASHI Y, TATENO S, SADA M, KASHIWAGI N: Strong association of HLA-DR4 with benign IgA nephropathy. *Nephron* 32:222–226, 1982

29. BERTHOUX FC, ALAMARTINE E, LAURENT B, BERTHOUX P, VACHEROT C, LAMBERT C, LE PETIT J-C: Primary IgA glomerulonephritis and MHC revisited. *Contrib Nephrol* 104:54–60, 1993
30. FREEDMAN BI, SPRAY BJ, HEISE ER: HLA associations in IgA nephropathy and focal and segmental glomerulosclerosis. *Am J Kidney Dis* 23:352–357, 1994
31. CLARKSON AR, SEYMOUR AE, THOMPSON AJ, HAYNES WDG, CHAN Y-L, JACKSON B: IgA nephropathy: A syndrome of uniform morphology, diverse clinical features and uncertain prognosis. *Clin Nephrol* 8:458–471, 1977
32. WALSHE JJ, BRENTJENS JP, COSTA GG, ANDRES GA, VENUTO RC: Abdominal pain associated with IgA nephropathy. *Am J Med* 77:765–767, 1984
33. NICHOLLS K, WALKER RG, DOWLING JP, KINCAID-SMITH P: "Malignant" IgA nephropathy. *Am J Kidney Dis* 5:42–46, 1985
34. WELCH TR, MCADAMS AJ, BERRY A: Rapidly progressive IgA nephropathy. *Am J Dis Child* 142:789–793, 1988
35. Southwest Pediatric Nephrology Study Group: A multicenter study of IgA nephropathy in children. *Kidney Int* 22:643–652, 1982
36. LEVY M, GONZALEZ-BURCHARD G, BROYER M, DOMMERGUES JP, FOULARD M, SOREZ JP, HABIB R: Berger's disease in children. *Medicine* 64:157–180, 1985
37. MUSTONEN J, PASTERNACK A: Associated diseases in IgA nephropathy, in *IgA Nephropathy,* edited by CLARKSON AR, Boston, Martin Nijhoff Publishing, 1987, pp 47–65
38. KIMMEL PL, PHILLIPS TM, FERREIRA-CENTENO A, FARKAS-SZALLASI T, ABRAHAM AA, GARRETT CT: Idiotypic IgA nephropathy in patients with human immunodeficiency virus infection. *N Engl J Med* 327:702–706, 1992
39. KATZ A, BARGMAN JM, MILLER DC, GUO J-W, SALEH GHALI V, SCHOENEMAN MJ: IgA nephritis in HIV-positive patients: A new HIV-associated nephropathy? *Clin Nephrol* 38:61–68, 1992
40. ROTH DA, WILZ DR, THEIL GB: Schoenlein-Henoch syndrome in adults. *Quart J Med* 55:145–152, 1985
41. HYMAN LR, WAGNILD JP, BEIRNE GJ, BURKHOLDER PM: Immunoglobulin-A distribution in glomerular disease: Analysis of immunofluorescence localization and pathogenetic significance. *Kidney Int* 3:397–408, 1973
42. MCCOY RC, ABRAMOWSKY CR, TISHER CC: IgA nephropathy. *Am J Pathol* 76:123–144, 1974
43. LEVY M, BEAUFILS H, GUBLER MC, HABIB R: Idiopathic recurrent macroscopic haematuria and mesangial IgA-IgG deposits in children (Berger's disease). *Clin Nephrol* 1:63–69, 1973
44. JENNETTE JC: The immunohistology of IgA nephropathy. *Am J Kidney Dis* 12:348–352, 1988
45. LAI KN: The cellular immunity and nature of IgA molecules in IgA nephropathy. *Contrib Nephrol* 104:99–111, 1993
46. TOMINO Y, SAKAI H, ENDOH M, MIURA M, SUGA T, KANESHIGE H, NOMOTO Y: Cross-reactivity of eluted antibodies from renal tissues of patients with Henoch-Schönlein purpura nephritis and IgA nephropathy. *Am J Nephrol* 3:315–318, 1983
47. MONTOLIU J, DARNELL A, TORRAS A, LENS XM, REVERT L: Absence of IgA in the glomerular deposits of patients with cirrhosis of the liver and glomerulopathy. *Proc Eur Dial Transplant* 22:784–789, 1985
48. D'AMICO G: Clinical features and natural history in adults with IgA nephropathy. *Am J Kidney Dis* 12:353–357, 1988
49. LAI K-N, CHUI S-H, LAI FM, LAM CWK: Predominant synthesis of IgA with lambda light chain in IgA nephropathy. *Kidney Int* 33:584–589, 1988
50. GALLA JH, SPOTSWOOD M, HARRISON LA, MESTECKY J: Urinary immunoglobulins in IgA-nephropathy and Henoch-Schoenlein purpura. *J Clin Immunol* 5:298–306, 1985
51. ZIMMERMAN SW, BURKHOLDER PM: Immunoglobulin A nephropathy. *Arch Int Med* 135:1217–1223, 1975
52. JULIAN BA, WYATT RJ, MCMORROW RG, GALLA JH: Serum complement proteins in IgA nephropathy. *Clin Nephrol* 20:251–258, 1983
53. WYATT RJ: The complement system in IgA nephropathy and Henoch-Schoenlein purpura: Functional and genetic aspects. *Contrib Nephrol* 104:82–91, 1993
54. CEDERHOLM B, WIESLANDER J, BYGREN P, HEINGARD D: Circulating complexes containing IgA and fibronectin in patients with primary IgA nephropathy. *Proc Natl Acad Sci USA* 85:4865–4868, 1988
55. JENNETTE JC, WIESLANDER J, TUTTLE R, FALK RJ: IgA-fibronectin aggregates in patients with IgA nephropathy and Henoch-Schönlein purpura. Diagnostic value and pathologic implications. *Am J Kidney Dis* 18:460–471, 1991
56. BALDREE LA, WYATT RJ, JULIAN BA, FALK RJ, JENNETTE JC: Immunoglobulin A-fibronectin aggregate levels in children and adults with immunoglobulin A nephropathy. *Am J Kidney Dis* 22:1–4, 1993
57. SHEN G, RITTENHOUSE HG, HAWKINS B, CHENG IKP, PETER JB: Detection of IgA-Fn aggregates in Chinese patients with IgA nephropathy and glomerulonephritis. (abstract) *J Am Soc Nephrol* 2:604, 1991
58. DAVIN JC, LI VECCHI M, NAGY J, FOIDART JM, FOIDART JB, BARBAGALLO, SANGIORGI G, MALAISE M, MAHIEU P: Evidence that the interaction between circulating IgA and fibronectin is a normal process enhanced in primary IgA nephropathy. *J Clin Immunol* 11:78–94, 1991
59. FLOEGE J, EITNER F, SCHULZE M, BRUNCKHORST R, SCHMIDT RE, KOCH KM: Plasma IgA-fibronectin complexes (IgA-FN-C) in IgA nephropathy patients: An artifact? (abstract) *J Am Soc Nephrol* 4:677, 1993
60. O'DONOGHUE DJ, NUSBAUM P, NOEL LH, HALBWACHS-MECARELLI L, LESAVRE P: Antineutrophil cytoplasmic antibodies in IgA nephropathy and Henoch-Schönlein purpura. *Nephrol Dial Transplant* 7:534–538, 1992
61. CZERKINSKY C, CRAGO SS, KOOPMAN WJ, JACKSON S, SCHROHENLOHER RE, GALLA J, MESTECKY J: The occurrence of circulating IgA-IgG immune complexes in IgA associated renal diseases, in *Mucosal Immunity, IgA and Polymorphonuclear Neutrophils,* edited by REVILLARD JP, VIOSIN C, WIERZBICKI N, Suresnes France, Foundation Francoallemande, 1985, pp 295–297
62. CZERKINSKY C, KOOPMAN WJ, JACKSON S, COLLINS JE, CRAGO SS, SCHROHENLOHER RE, JULIAN BA, GALLA JH, MESTECKY J: Circulating immune complexes and immunoglobulin A rheumatoid factor in patients with mesangial immunoglobulin A nephropathies. *J Clin Invest* 77:1931–1938, 1986
63. SAULSBURY FT: IgA rheumatoid factor in Henoch-Schoenlein purpura. *J Pediatr* 108:71–76, 1986
64. BAART DE LA FAILLE-KUYPER EH, KATER L, KUIJTEN RH, KOOIKER CJ, WAGENAAR SS, VAN DER ZOUWEN P, DOURHOUT MEES EJ: Occurrence of vascular IgA deposits in clinically normal skin of patients with renal disease. *Kidney Int* 9:424–429, 1976
65. HASBARGEN JA, COPLEY JB: Utility of skin biopsy in the diagnosis of IgA nephropathy. *Am J Kidney Dis* 6:100–102, 1985
66. LAMM ME, EMANCIPATOR SN, GALLO GR: Relevance of an experimental model to clinical IgA nephropathy. *Contrib Nephrol* 40:32–36, 1984
67. RIFAI A, SMALL P JR, AYOUB EM: Experimental IgA nephropathy. *Contrib Nephrol* 40:37–44, 1984
68. SCIVITTARO V, AMORE A, EMANCIPATOR SN: Animal models as a means to study IgA nephropathy. *Contrib Nephrol* 104:65–78, 1993
69. DE HEER E, GORTER A, VAN DER WAL AM, VAN EDENBURG JDH, ROZING J, BRUJIN JA, DAHA MR: Induction of microhematuria by an IgA isotype switch variant of a monoclonal anti-Thy-1 antibody in the rat (abstract). *J Am Soc Nephrol* 4:599, 1993
70. COPPO R: The pathogenetic potential of environmental antigens in IgA nephropathy. *Am J Kidney Dis* 12:420–424, 1988
71. DELACROIX DL, ELKON KB, GEUBEL AP, HODGSON HF, DIVE C, VAERMAN JP: Changes in size, subclass, and metabolic properties of serum immunoglobulin A in live diseases and in other diseases with high serum immunoglobulin A. *J Clin Invest* 71:358–367, 1983
72. VAN DEN WALL BAKE AWL, DAHA MR, VAN DER ARK A, HIEMSTRA PS, RADL J, VAN ES LA: Serum levels and in vitro production of IgA subclasses in patients with primary IgA nephropathy. *Clin Exp Immunol* 74:115–120, 1988
73. VAN DEN WALL BAKE AWL, DAHA MR, EVERS-SCHOUTEN J, VAN ES LA: Serum IgA and the production of IgA by peripheral blood and bone marrow lymphocytes in patients with primary IgA nephropathy: Evidence for the bone marrow as a source of mesangial IgA. *Am J Kidney Dis* 12:410–414, 1988
74. LAYWARD L, ALLEN AC, HATTERSLEY JM, HARPER SJ, FEEHALLY J: Elevation of IgA in IgA nephropathy is localized to the serum and not saliva and is restricted to IgA1 subclass. *Nephrol Dial Transplant* 8:25–28, 1993

75. LAYWARD L, FINNEMORE AM, ALLEN AC, HARPER SJ, FEEHALLY J: Systemic and mucosal IgA responses to systemic antigen challenge in IgA nephropathy. *Clin Immunol Immunopathol* 69:306–313, 1993
76. BROWN TA, CLEMENTS ML, MURPHY BR, RADL J, HAAIJMAN JJ, MESTECKY J: Molecular form and subclass distribution of IgA antibodies after immunization with live and inactivated influenza vaccine. *Adv Exp Med Biol* 216B:1691–1700, 1987
77. SANCHO J, EGIDO J, RIVERA F, HERNANDO L: Immune complexes in IgA nephropathy: Presence of antibodies against diet antigens and delayed clearance of specific polymeric IgA immune complexes. *Clin Exp Immunol* 54:194–202, 1983
78. COPPO R, AMORE A, ROCCATELLO D: Dietary antigens and primary immunoglobulin A nephropathy. *J Am Soc Nephrol* 2:S173–S180, 1992
79. RUSSELL MW, MESTECKY J, JULIAN BA, GALLA JH: IgA-associated renal diseases: Antibodies to environmental antigens in sera and deposition of immunoglobulins and antigens in glomeruli. *J Clin Immunol* 6:74–86, 1986
80. ROSTOKER G, PETIT-PHAR M, DEL PRATO S, TERZIDIS H, LANG P, DUBERT JM, WEIL B, LAGRUE G: Mucosal immunity in primary glomerulonephritis: II. Study of the serum IgA subclass repertorie to food and airborne antigens. *Nephron* 59:561–566, 1991
81. ANDRÉ C, BERTHOUX FC, ANDRÉ F, GILLON J, GENIN C, SABATIER J-C: Prevalence of IgA2 deposits in IgA nephropathies: A clue to their pathogenesis. *N Engl J Med* 303:1343–1346, 1980
82. CONLEY ME, COOPER MD, MICHAEL AF: Selective deposition of immunoglobulin A1 in immunoglobulin A nephropathy, anaphylactoid purpura nephritis, and systemic lupus erythematosus. *J Clin Invest* 66:1432–1436, 1980
83. TOMINO Y, ENDOH M, NOMOTO Y, SAKAI H: Immunoglobulin A1 in IgA nephropathy. *N Engl J Med* 305:1159–1160, 1981
84. LOMAX-SMITH JD, ZABROWARNY LA, HOWARTH GS, SEYMOUR AE, WOODROFFE AJ: The immunochemical characterization of mesangial IgA deposits. *Am J Pathol* 113:359–364, 1983
85. RAJARAMAN S, GOLDBLUM RM, CAVALLO T: IgA-associated glomerulonephritides: A study with monoclonal antibodies. *Clin Immunol Immunopathol* 39:514–522, 1986
86. KOMATSU N, NAGURA H, WATANABE K, NOMOTO Y, KOBAYASHI K: Mesangial deposition of J chain-linked polymeric IgA in IgA nephropathy. *Nephron* 33:61–64, 1983
87. EGIDO J, SANCHO J, MAMPASO F, LOPEZ-TRASCASA M, SANCHEZ-CRESPO M, BLASCO R, HERNANDO L: A possible common pathogenesis of the mesangial IgA glomerulonephritis in patients with Berger's disease and Schönlein-Henoch syndrome. *Proc Eur Dial Transplant Assoc* 17:660–666, 1980
88. VALENTIJN R, RADL J, HAAIJMAN J, VERMEER B, WEENING J, KAUFMANN RH, DAHA MR, VAN ES LA: Circulating and mesangial secretory component-binding IgA1 in primary IgA nephropathy. *Kidney Int* 26:760–766, 1984
89. MONTEIRO RC, HALBWACHS-MECARELLI L, ROQUE-BARREIRA MC, NOEL L-H, BERGER J, LESAVRE P: Charge and size of mesangial IgA in IgA nephropathy. *Kidney Int* 28:666–671, 1985
90. MESTECKY J, WALDO FB, BRITT WJ, JULIAN BA, TOMANA M, VAN DEN WALL BAKE AWL, RUSSELL MW, GALLA JH, MOLDOVEANU Z, JACKSON S: Exogenous antigens deposited in the glomeruli of patients with IgA nephropathy, in *Pathogenesis of IgA Nephropathy,* edited by SAKAI H, SAKAI O, NOMOTO Y, Tokyo, Harcourt Brace, 1991, pp 247–257
91. JACKSON S, MONTGOMERY RI, JULIAN BA, GALLA JH, CZERKINSKY C: Aberrant synthesis of antibodies directed at the Fab fragment of IgA in patients with IgA nephropathies. *Clin Immunol Immunopathol* 45:208–213, 1987
92. JACKSON S: Immunoglobulin-antiimmunoglobulin interactions and immune complexes in IgA nephropathy. *Am J Kidney Dis* 12:425–429, 1988
93. BÉNÉ M-C, CANTON P, AMEIL C, MAY T, FAURE G: Absence of mesangial IgA in AIDS: A postmortem study. *Nephron* 58:240–241, 1991
94. O'DONOGHUE DJ, DARVILL A, BALLARDIE FW: Mesangial cell autoantigens in immunoglobulin A nephropathy and Henoch-Schoenlein purpura. *J Clin Invest* 88:1522–1530, 1991
95. CHAN TM, FRAMPTON G, JAYNE DRW, PERRY GJ, LOCKWOOD CM, CAMERON JS: Clinical significance of anti-endothelial cell antibodies in systemic vasculitis: A longitudinal study comparing anti-endothelial cell antibodies and anti-neutrophil cytoplasmic antibodies. *Am J Kidney Dis* 22:387–392, 1993
96. WYATT RJ, JULIAN BA: Activation of complement in IgA nephropathy. *Am J Kidney Dis* 12:437–442, 1988
97. WAXMAN FJ, HEBERT LA, COSIO FG, SMEAD WL, VANAMAN ME, TAGUIAM JM, BIRMINGHAM DJ: Differential binding of immunoglobulin A and immunoglobulin G1 immune complexes to primate erythrocytes in vivo. *J Clin Invest* 77:82–89, 1986
98. LAI KN, LAI FM, CHUI SH, CHAN YM, TSAO GS, LEUNG KN, LAM CWK: Studies of lymphocyte subpopulations and immunoglobulin production in IgA nephropathy. *Clin Nephrol* 28:281–287, 1987
99. SAKAI H, MIYAZAKI M, ENDOH M, NOMOTO Y: Increase in IgA-specific switch T cells in patients with IgA nephropathy. *Clin Exp Immunol* 78:378–382, 1989
100. LAYWARD L, ALLEN AC, HATTERSLEY JM, HARPER SJ, FEEHALLY J: Deficiency of IgG subclass antibody response to tetanus toxoid associated with high serum IgA levels in IgA nephropathy. *Clin Nephrol* 40:131–136, 1993
101. DEMAINE AG, RAMBAUSEK M, KNIGHT JF, WILLIAMS DG, WELSH KI, RITZ E: Relation of mesangial IgA glomerulonephritis to polymorphism of immunoglobulin heavy chain switch region. *J Clin Invest* 81:611–614, 1988
102. FEEHALLY J, BEATTIE TJ, BRENCHLEY PEC, COUPES BM, MALLICK NP, POSTLETHWAITE RJ: Sequential study of the IgA system in relapsing IgA nephropathy. *Kidney Int* 30:924–931, 1986
103. BANNISTER KM, DREW PA, CLARKSON AR, WOODROFFE AJ: Immunoregulation in glomerulonephritis, Henoch-Schönlein purpura and lupus nephritis. *Clin Exp Immunol* 53:384–390, 1983
104. SCHENA FP, MASTROLITTI G, FRACASSO AR, PASTORE A, LADISA N: Increased immunoglobulin-secreting cells in the blood of patients with active idiopathic IgA nephropathy. *Clin Nephrol* 26:163–168, 1986
105. HALE GM, MCINTOSCH SL, HIKI Y, CLARKSON AR, WOODROFFE AJ: Evidence for IgA-specific B cell hyperactivity in patients with IgA nephropathy. *Kidney Int* 29:718–724, 1986
106. JACKSON S, GALLA JH, KIRK KA, THORN BT, JULIAN BA: Epstein-Barr virus transformation of B lymphocytes from IgA nephropathy patients and first-degree relatives results in increased immunoglobulin synthesis not restricted to IgA. *Am J Kidney Dis* 17:55–61, 1991
107. GONZALEZ-CABRERO J, DE NICHOLAS R, HERNANDO L, EGIDO J: Expression and synthesis of cross-reactive antibodies by peripheral blood lymphocytes and their suppression by antiidiotypes in patients with IgA nephropathy. *J Immunol* 147:4162–4166, 1991
108. VAN DEN WALL BAKE AWL: Mechanisms of IgA deposition on the mesangium. *Contrib Nephrol* 104:138–146, 1993
109. VAN DEN WALL BAKE AWL, BRUIJN JA, ACCAVITTI MA, CROWLEY-NOVICK PA, SCHROHENLOHER RE, JULIAN BA, JACKSON S, KUBAGAWA H, COOPER MD, DAHA MR, MESTECKY J: Shared idiotypes in mesangial deposits in IgA nephropathy are not disease-specific. *Kidney Int* 44:65–74, 1993
110. TOMANA M, KULHAVY R, MESTECKY J: Receptor-mediated binding and uptake of immunoglobulin A by human liver. *Gastroenterology* 94:762–770, 1988
111. MESTECKY J, TOMANA M, CROWLEY-NOWICK PA, MOLDOVEANU Z, JULIAN BA, JACKSON S: Defective galactosylation and clearance of IgA1 molecules as a possible etiopathogenic factor in IgA nephropathy. *Contrib Nephrol* 104:172–182, 1993
112. DAVIN JC, MALAISE M, FOIDART J, MAHIEU P: Anti-α-galactosyl antibodies and immune complexes in children with Henoch-Schönlein purpura or IgA nephropathy. *Kidney Int* 31:1132–1139, 1987
113. JULIAN BA, CANNON VR, WALDO FB, EGIDO J: Macroscopic hematuria and proteinuria preceding renal IgA deposition in patients with IgA nephropathy. *Am J Kidney Dis* 17:472–479, 1991
114. CHAUVEAU D, DROZ D: Follow-up evaluation of the first patients with IgA nephropathy described at Necker Hospital. *Contrib Nephrol* 104:1–5, 1993
115. D'AMICO G, RAGNI A, GANDINI E, FELLIN G: Typical and atypical natural history of IgA nephropathy in adult patients. *Contrib Nephrol* 104:6–13, 1993
116. WYATT RJ, JULIAN BA, WOODFORD SY, WANG C, ROBERTS J, THOMPSON JS, CHRISTENSON MJ, MCLEAN RH: C4A deficiency and

poor prognosis in patients with IgA nephropathy. *Clin Nephrol* 36:1–5, 1991
117. BERTHOUX FC, ALAMARTINE E, POMMIER G, LE PETIT J-C: HLA B35 antigen as a prognostic factor. *N Engl J Med* 319:1609–1610, 1988
118. GLASSOCK RJ: Treatment of immunologically mediated glomerular disease. *Kidney Int* 42:S121–S126, 1993
119. CLARKSON AR, WOODROFFE AJ, BANNISTER KM, ODUM J: Therapy in IgA nephropathy. *Contrib Nephrol* 104:189–197, 1993
120. LAI KN, LAI FM, HO CP, CHAN KW: Corticosteroid therapy in IgA nephropathy with nephrotic syndrome: A long-term controlled trial. *Clin Nephrol* 26:174–180, 1986
121. KOBAYASHI Y, FUJII K, HIKI Y, TATENO S, KUROKAWA A, KAMIYAMA M: Steroid therapy in IgA nephropathy: A retrospective study in heavy proteinuric cases. *Nephron* 48:12–17, 1988
122. WALDO FB, ALEXANDER R, WYATT RJ, KOHAUT EC: Alternate-day prednisone therapy in children with IgA-associated nephritis. *Am J Kidney Dis* 13:55–60, 1989
123. JULIAN BA, BARKER C: Alternate-day prednisone therapy in IgA nephropathy. *Contrib Nephrol* 104:198–206, 1993
124. JULIAN BA, BARKER CV, WOODFORD SY: Alternate-day prednisone treatment of patients with IgA nephropathy. (abstract) *J Am Soc Nephrol* 4:681, 1993
125. SCHENA FR, MONTENEGRO M, SCIVITTARO V: Meta-analysis of randomized controlled trials in patients with IgA nephropathy (Berger's disease). *Nephrol Dial Transplant* 5 (Suppl 1):47–52, 1990
126. SOUTHWEST PEDIATRIC NEPHROLOGY STUDY GROUP: Association of IgA nephropathy with steroid-responsive nephrotic syndrome. *Am J Kidney Dis* 5:157–164, 1985
127. HOGG RJ, SAVINO DA: Spontaneous remission of nephrotic syndrome in a patient with IgA nephropathy. *Pediatr Nephrol* 4:36–38, 1990
128. WOO KT, EDMUNDSON RPS, YAP HK, WU AYT, CHIANG GSC, LEE EJC, PWEE HS, LIM CH: Effects of triple therapy on the progression of mesangial proliferative glomerulonephritis. *Clin Nephrol* 27:56–64, 1987
129. WOO KT, CHIANG GSC, LIM CH: Follow-up renal biopsies in IgA nephritic patients on triple therapy. *Clin Nephrol* 27:304–305, 1987
130. WALKER RG, YU SH, OWEN JE, KINCAID-SMITH P: The treatment of mesangial IgA nephropathy with cyclophosphamide, dipyridamole, and warfarin: A two year prospective trial. *Clin Nephrol* 34:103–107, 1990
131. LAI KN, LAI FM, LI PKT, VALLANCE-OWEN J: Cyclosporin treatment of IgA nephropathy: A short-term controlled trial. *Brit Med J* 295:1165–1168, 1987
132. MIURA M, ENDOH M, NOMOTO Y, SAKAI H: Long-term effect of urokinase therapy in IgA nephropathy. *Clin Nephrol* 32:209–216, 1989
133. BÉNÉ MC, HURAULT DE LIGNY B, KESSLER M, FOLIGUET B, FAURE GC: Tonsils in IgA nephropathy. *Contrib Nephrol* 104:153–161, 1993
134. HOLMAN RT, JOHNSON SB, BIBUS D, SPENCER DC, DONADIO JV: Essential fatty acid deficiency profiles in idiopathic immunoglobulin A nephropathy. *Am J Kidney Dis* 23:648–654, 1994
135. ROSTOKER G, PECH M-A, DEL PRATO S, PETIT-PHAR M, BEN MAADI A, DUBERT JM, LANG P, WEIL B, LAGRUE G: Serum IgG subclasses and IgM imbalances in adult IgA mesangial glomerulonephritis and idiopathic Henoch-Schoenlein purpura. *Clin Exp Immunol* 75:30–34, 1989
136. ROSTOKER G, DESVAUX-BELGHITI D, PILATTE Y, PETIT-PHAR M, PHILLPON C, DESFORGES L, TERZIDIS H, INTRATOR L, ANDRE C, ADNOT S, BONIN P, BIERLING P, REMY P, LAGRUE G, WEIL B: High-dose immunoglobulin therapy for severe IgA nephropathy and Henoch-Schoenlein purpura. *Ann Int Med* 120:476–484, 1994
137. REKOLA S, BERGSTRAND L, BUCHT H: Deterioration rate in hypertensive IgA nephropathy: Comparison of a converting enzyme inhibitor and β blocking agents. *Nephron* 59:57–60, 1991
138. CATTRAN DC, GREENWOOD C, RITCHIE S: Long-term benefit of angiotensin-converting enzyme inhibitor therapy in patients with severe immunoglobulin A nephropathy: A comparison to patients receiving treatment with other antihypertensive agents and to patients receiving no therapy. *Am J Kidney Dis* 23:247–254, 1994
139. CAMERON JS: The future of nephrology with special regard to advances in treatment. *Kidney Int* 42:S203–S214, 1992
140. COUSER WG: Research opportunities and future directions in glomerular disease. *Semin Nephrol* 13:457–471, 1993
141. BERGER J: Recurrence of IgA nephropathy in renal allografts. *Am J Kidney Dis* 12:371–372, 1988
142. BACHMAN U, BIAVA C, AMEND W, FEDUSKA N, MELZER J, SALVATIERRA O, VINCENTI F: The clinical course of IgA nephropathy and Henoch-Schönlein purpura following renal transplantation. *Transplantation* 42:511–515, 1986
143. WEISS JH, BHATHENA DB, CURTIS JJ, LUCAS BA, LUKE RG: A possible relationship between Henoch-Schoenlein syndrome and IgA nephropathy (Berger's disease): An illustrative case. *Nephron* 22: 582–589, 1978
144. SILVA FG, CHANDER P, PIRANI CL, HARDY MA: Disappearance of glomerular mesangial IgA deposits after renal allograft transplantation. *Transplantation* 33:214–216, 1982
145. ODUM J, PEH CA, CLARKSON AR, BANNISTER KM, SEYMOUR AE, GILLIS D, THOMAS AC, MATHEW TH, WOODROFFE AJ: Recurrent mesangial IgA nephritis following renal transplantation. *Nephrol Dial Transplant* 9:309–312, 1994
146. MITSUISHI Y, CECKA JM: Disease effects and association, in *Clinical Transplants 1992* edited by TERASAKI PI, CECKA JM, Los Angeles, UCLA Tissue Typing Laboratory, 1993, pp 371–381
147. LIM EC, CHAI D, GJERTSON DW, KOKA P, TERASAKI PI: In vitro studies to explain high renal allograft survival in IgA nephropathy patients. *Transplantation* 55:996–999, 1993
148. COSIO FG, FALKENHAIN M, CARLTON S, COSIO MJ: Association of thin glomerular basement membrane nephropathy (TGBM) with other glomerulopathies. (abstract) *J Am Soc Nephrol* 4:261, 1993