

SPECIAL ARTICLE

Hypothesis: Dysregulation of Immunologic Balance Resulting From Hygiene and Socioeconomic Factors May Influence the Epidemiology and Cause of Glomerulonephritis Worldwide

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● Glomerular diseases show diverse epidemiological characteristics throughout the world, which has been suggested to be caused by differences in genetics of the underlying populations or environmental exposure to the putative antigens or agents that either trigger or induce the disease. Recently, an alteration in immune balance of the T helper 1 (T_H1) and T helper 2 (T_H2) subsets has been implicated as a mechanism to explain the relative increase in allergic diseases in industrialized nations. According to the Hygiene Hypothesis, overcrowding and poor hygiene early in life may protect from atopic diseases because exposure to microbes predisposes in favor of a T_H1-dominant response. Conversely, dominance of the T_H2 subset would be responsible for the increasing incidence of allergies. We present the hypothesis that this imbalance may help explain the predilection for membranoproliferative glomerulonephritis (GN) and mesangial proliferative GN to be associated with developing and/or poor nations, whereas immunoglobulin A nephropathy and minimal change disease are observed more commonly in industrialized nations. The implication of the Hygiene Hypothesis is that clinical expression of immune-mediated renal disease would depend on the prevailing T_H1/T_H2 balance, rather than the etiologic agent, and it may help explain the epidemiological pattern of glomerular diseases worldwide. *Am J Kidney Dis* 42:575-581.

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INDEX WORDS: Glomerulonephritis (GN); epidemiology; cell-mediated immunity; T helper (T_H) cell (CD4) subsets; hygiene hypothesis.

RECENTLY, WE conducted a study of the epidemiological pattern of glomerular disease in Lima, Peru, and found that membranoproliferative glomerulonephritis (MPGN) was the most common primary glomerular disease, accounting for more than 25% of all cases, whereas immunoglobulin A (IgA) nephropathy was distinctly uncommon and amounted to less than 2% of all cases.¹ This pattern is similar to that observed in Africa,²⁻⁴ but is distinct from that observed in industrialized countries, where IgA nephropathy is one of the more common glomerular diseases and MPGN is less frequent.⁵ Furthermore, unlike the United States and Japan, where many cases of MPGN are caused by chronic hepatitis C virus (HCV) infection,^{6,7} in Peru, MPGN was not associated with HCV infection.¹ Although this suggests a different etiologic agent may be responsible for MPGN in Peru, we propose in this article that the inherent susceptibility to glomerular disease may not rely as much on the antigen as it does on host response, and this may be controlled largely by environmental factors, in addition to the accepted role of genetic mechanisms.

CELL-MEDIATED IMMUNITY IS REGULATED BY T HELPER CELL SUBSETS

The immune system is controlled largely by T helper (T_H) cells (CD4⁺ cells). The principal function of CD4⁺ cells expressing the T_H1 phenotype is the immune response to infection. These cells are responsible for the induction of cell-mediated organ-specific immunity and the generation of complement-fixing antibody, and the process is orchestrated by the release of interleukin-12 (IL-12) from activated macrophages, interferon- γ (IFN- γ) from natural killer cells, and activation of CD4⁺ cells to express

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Received March 27, 2003; accepted in revised form May 20, 2003.

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0272-6386/03/4203-0025\$30.00/0

doi:10.1016/S0272-6386(03)00801-1

IL-2. CD4⁺ cells expressing the T_H2 phenotype are more important in the development of allergy and generation of IgE, IgA, and non-complement-fixing IgG (especially subtype IgG4), and the process is mediated by IL-4, IL-5, IL-6, IL-10, and IL-13. T_H1 and T_H2 counterregulate each other because IFN- γ inhibits the T_H2 response and IL-10 can block T_H1 actions; however, both T_H1 and T_H2 also can be activated simultaneously.⁸ In this regard, a third CD4⁺ cell that also expresses the IL-2 α receptor (CD25) appears to have an important regulatory role in silencing T_H1 and T_H2 action, both through direct cell contact and by releasing IL-10 and transforming growth factor- β .⁹⁻¹³

Normally, we are born with a T_H2-dominant phenotype, which may be carried over from the mother as a means to minimize a vigorous immune response between the mother and fetus.¹⁴ Studies have found that IL-12 production by macrophages and IFN- γ production by natural killer cells is relatively impaired in the neonate, leading to a reduced T_H1 response.¹⁵ Conversely, IL-4 and IL-13 levels are relatively high, consistent with a T_H2-dominant response.¹⁶ Some CD4⁺ CD25⁺ cells also are present.¹¹ Although the neonatal period is characterized by a T_H2 phenotype, exposure to a variety of antigens during or after the neonatal period can convert the immune phenotype to favor a T_H1-dependent state. Alternatively, lack of exposure to bacterial antigens, particularly during the first 1 or 2 years of life, may favor a persistent T_H2-dependent phenotype.¹⁷ Based on these observations, the Hygiene Hypothesis has been developed to explain the increasing frequency of allergies in industrialized nations.

THE HYGIENE HYPOTHESIS AS A MECHANISM TO EXPLAIN THE INCREASING FREQUENCY OF ALLERGIES IN INDUSTRIALIZED NATIONS

The Hygiene Hypothesis originally was proposed as a mechanism to explain the marked increase in allergies observed in industrialized (Westernized) societies.¹⁸⁻²⁵ Specifically, the hypothesis proposes that early and frequent exposure to bacterial and other antigens, common in developing nations, leads to a normal T_H1 response, but that the better public hygiene and less infections observed in industrialized nations

may lead to persistence of the T_H2 phenotype and thereby increase our risk for developing allergies.

Several lines of evidence support this hypothesis. First, it is known that allergy (which has a T_H2 phenotype) is less common in situations in which exposure to infections is more common, such as observed in situations of lower socioeconomic status, larger families, lower birth order, and participation in day care.^{18,22} Similarly, several studies also reported that infection early in life with measles or hepatitis A may protect individuals from developing allergy in adulthood.^{23,24} Immunization with bacillus Calmette-Guérin can also induce a T_H1 response and delayed-type hypersensitivity response to mycobacterial antigens, and it has been reported that children administered bacillus Calmette-Guérin, particularly during the first year of life, also are protected from allergy in adulthood provided they maintain the delayed-type hypersensitivity-response.²⁵

CAN THE HYGIENE HYPOTHESIS EXPLAIN THE EPIDEMIOLOGICAL PATTERNS OF GLOMERULAR DISEASE OBSERVED WORLDWIDE?

Studies largely led by Holdsworth et al²⁶ have shown that most proliferative glomerular diseases are driven by a T_H1 response. One might then hypothesize that such diseases as MPGN, mesangial proliferative glomerulonephritis (GN; of the non-IgA type), and poststreptococcal GN may be more frequent in developing countries. MPGN is one of the most common glomerular diseases in Africa (such as Nigeria),^{3,4} the West Indies (Trinidad),²⁷ eastern Europe (Poland),²⁸ Turkey,²⁹ and east China.³⁰ In South America, MPGN in adults is very common, particularly in countries with a lower socioeconomic status (Fig 1A). Conversely, MPGN is infrequent in the United States, Japan, and Europe (Spain and France), and in these countries, the incidence appears to be decreasing.³¹⁻³⁵

Similarly, mesangial proliferative GN (non-IgA type) is very common in Africa, including Zimbabwe and Namibia,^{36,37} as well as South America,¹ the West Indies,²⁷ and China, particularly during the 1970s and 1980s.^{30,38} In South America, non-IgA mesangial proliferative GN is more common in Peru (frequency, 11.8%) and

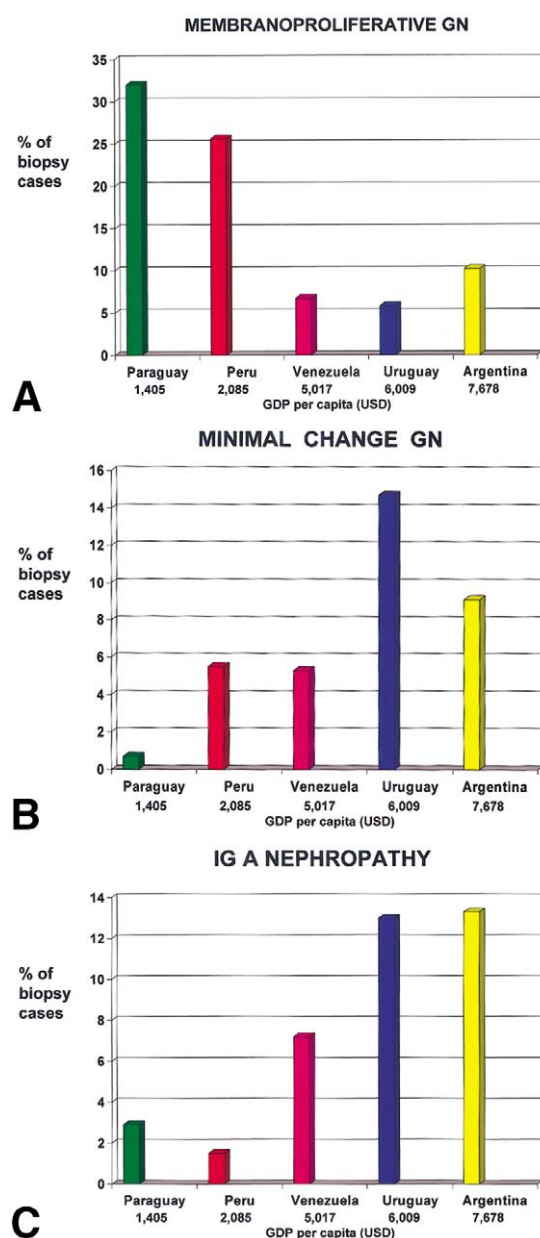


Fig 1. Epidemiology of glomerular disease in selected South American countries based on the gross national product. Percentage of primary glomerular diseases in adult patients caused by (A) MPGN, (B) minimal change disease, and (C) IgA nephropathy. With increasing gross national product, the frequency of MPGN decreases, whereas the frequency of minimal change disease and IgA nephropathy increases. All biopsies included immunofluorescence. Data for Argentina, from Di Gioia et al⁸⁴; for Paraguay, from Dr Elena Kasamatsu, Instituto de Investigaciones en Ciencias de la Salud (IICS) de la Universidad Nacional de Asunción; for Venezuela, Dr Atahualpa Pinto, Universidad Central de Venezuela; for Uruguay, Caorsi et al.⁸⁵

Paraguay (frequency, 37.6%) than Uruguay (frequency, 3.4%), possibly reflecting the better socioeconomic status of the latter country (Drs E. Kasamatsu and N. Mazzuchi, personal communication, April 2003). Mesangial proliferative GN (non-IgA type) also is common among Southwestern American Indians and Australian Aborigines.³⁹ Poststreptococcal glomerular disease also is more common in developing countries, including Africa, the West Indies, South Africa, India, and South America.²

Conversely, minimal change disease may be an example of T_H2 -dependent glomerular disease. It frequently is associated with atopy (including pollen allergy, seasonal allergy, urticaria, and atopic dermatitis),⁴⁰⁻⁴³ elevated IgE levels,⁴⁴⁻⁴⁸ and elevated IL-4 levels in peripheral T cells,⁴⁹⁻⁵² although there also can be elevations in levels of some T_H1 cytokines.^{51,52} Some patients with minimal change disease have gone into remission after measles infection.⁵³ Furthermore, consistent with the Hygiene Hypothesis, minimal change disease is rare in Africa (including Nigeria, Namibia, Zimbabwe, and Tunisia) and South America^{2,4,37} despite its marked frequency in the United States and Europe.³⁵ Similarly, in South America, minimal change disease is much less common in adults in countries of lower socioeconomic status (Fig 1B).

IgA nephropathy is another glomerular disease that likely is T_H2 dependent. Although occasional studies find evidence for some T_H1 activation in IgA nephropathy,^{54,55} the majority of studies have found that the principal cytokines produced by circulating T cells are IL-4, IL-5, IL-6, IL-10, and IL-13, all T_H2 -dependent cytokines.⁵⁴⁻⁵⁷ IgA production is driven by IL-5, a T_H2 cytokine.⁵⁸ There also is evidence that T_H2 cytokines can alter glycosylation of IgA,⁵⁹ known to be a key factor in its pathogenesis.⁶⁰ Furthermore, experimental IgA nephropathy is much more severe and is associated with more abnormalities in IgA glycosylation in mice that have a predominant T_H2 response (Balb/c) compared with control (C3HeB) mice.⁶¹ Some patients with IgA nephropathy also manifest atopy^{62,63} and elevated IgE levels,^{46,64} and others develop IgA antibodies to food antigens.⁶⁵ Some patients with IgA nephropathy also may develop steroid-sensitive nephrotic syndrome, consistent with superimposed minimal change disease, which

further suggests that these individuals are in a T_H2-dependent state.⁶⁶

It thus is of interest that IgA nephropathy is extremely rare in Africa, such as in Tunisia and Zimbabwe.^{2,36} IgA nephropathy also is uncommon in Pakistan and India, where it represents approximately 5% of total glomerular disease.² In South America, IgA nephropathy also is rare¹ and shows a similar pattern, in which its frequency is markedly lower in countries of lower socioeconomic status (Fig 1C).

Conversely, IgA nephropathy is present in 40% to 50% of all primary GN in Japan, Singapore, and Hong Kong⁵; it is relatively less frequent in Malaysia and Thailand, where it accounts for 6% to 10% of primary GN.^{67,68} IgA nephropathy also is common in Europe, Australia, and the United States.⁵ In some countries, such as the United States and Spain, the frequency of IgA nephropathy is increasing.^{31,35}

THE RENAL HYGIENE HYPOTHESIS: SUMMARY, CAVEATS, AND FUTURE STUDIES

To summarize, we propose a new hypothesis to explain the divergent epidemiological characteristics of glomerular disease worldwide. Specifically, we suggest that the overall hygiene and socioeconomic status of a country may predispose its citizens to either a T_H1- or T_H2-dominant phenotype that will increase the susceptibility of that population to specific types of glomerular disease. Although recognizing that true incidence data are lacking, we present evidence that T_H1-dominant diseases, such as MPGN and non-IgA mesangial proliferative GN, are more common in biopsy series from poorer countries, such as in South America and Africa, whereas T_H2-dominant diseases, such as IgA nephropathy and minimal change disease, are more common in wealthier industrialized nations. We also reviewed evidence that in industrialized countries, the frequency of MPGN is decreasing, whereas such diseases as IgA nephropathy are increasing.

Although general trends for T_H1 and T_H2 dominance generally can be predicted by the Hygiene Hypothesis, it is important to recognize that many additional factors also modulate this balance. Thus, T_H2 can be induced by helminth infections^{69,70} and malnutrition,⁷¹⁻⁷³ both of which may be more likely to occur in less developed countries. Furthermore, psychological stress and

depression can induce T_H2 responses.⁷⁴⁻⁷⁸ Conversely, obesity, by virtue of increasing leptin levels, may be able to induce a T_H1 response.⁷³ Genetic factors also have an important role in the immune response. For example, there is evidence that IgA nephropathy is linked to a gene on chromosome 6.⁷⁹ Finally, T_H1 and T_H2 responses sometimes can be engaged simultaneously.⁸ Thus, dysregulation of the T_H1 and T_H2 response, which is mediated by a complexity of mechanisms, may be the critical factor that predisposes to glomerular disease. In this regard, a key means for the prevention of glomerular disease may be the stimulation and recruitment of IL-10-secreting regulatory (CD4⁺/CD25⁺) cells that can shift the immune balance back toward normal.⁸⁰

It is important to discuss alternative hypotheses on the varying epidemiological characteristics of glomerular disease. First is the hypothesis that different patterns of glomerular diseases may simply reflect differences in biopsy practices. This may be particularly true for IgA nephropathy because many of these patients have only mild renal disease characterized by microscopic hematuria and nonnephrotic proteinuria and hence would normally not undergo renal biopsy. One might posit that in wealthier countries, patients with asymptomatic disease may be more likely to undergo biopsy and therefore one might expect to see greater frequencies of IgA nephropathy diagnosed in these countries. It is thought that the high frequency of IgA nephropathy in Japan is caused by the common practice of performing biopsy on individuals with asymptomatic microhematuria and normal renal function discovered during the routine testing of students or workers.⁵ Although this latter observation may be one reason for the high frequency of IgA nephropathy in Japan, this policy is not routinely followed in other industrialized countries, where biopsy generally is reserved for individuals with nephritic syndrome, nephrotic syndrome, or asymptomatic proteinuria/microhematuria with deteriorating renal function. Interestingly, these latter criteria are similar to the indications for renal biopsy in such countries as Peru.¹ Hence, it appears that biopsy practices cannot completely explain the divergent epidemiological patterns of glomerular disease worldwide.

It also has been hypothesized that racial differences may account for geographic differences in

the frequency of IgA nephropathy, such that Asians may be more susceptible, whereas blacks may be less susceptible.^{5,35} This issue remains unresolved because although some studies suggest that IgA nephropathy is less common in African Americans,⁸¹ 2 studies found that the incidence of IgA nephropathy in African Americans was equivalent to that of Caucasians.^{82,83} This raises the possibility that the predisposition to IgA nephropathy may relate more to environmental than genetic mechanisms, although some genetic predisposition also is likely to be important.⁷⁹

Finally, a classic hypothesis is that the increased frequency of MPGN in developing countries is caused by the marked increase in incidence of bacterial infections in these countries and does not relate to alterations in T_H1/T_H2 balance. Although this hypothesis certainly is tenable, it is of interest that we were not able to pinpoint specific infections with any of the cases of MPGN noted in our series in Peru.¹ A striking finding was the general lack of evidence for such active infection as suggesting fever or recent respiratory or gastrointestinal illness.¹ This would favor the possibility that MPGN might result from an aberrant immune response to a relatively innocuous antigen, rather than a robust immune response to a virulent antigen. In this regard, this hypothesis could be expanded to the general concept that glomerular disease may represent an abnormal immune response to foreign antigens (resulting in such diseases as MPGN and IgA nephropathy) or self-antigens (which also could be triggered by foreign antigens and might result in such autoimmune diseases as Goodpasture's syndrome).

In conclusion, we propose a new hypothesis to explain the divergent epidemiological pattern of glomerular disease worldwide. The purpose of this report is not to provide proof of this hypothesis, but rather to stimulate studies that can directly and prospectively determine whether the imbalance in the immune system, driven by hygiene and other environmental and genetic factors, may underlie the pathogenesis of many frequently diagnosed glomerular disorders. Thus, it may not be the antigen that matters as much as the type of immune response to that antigen that determines the type of GN that one develops. Hence, a better understanding of how to achieve

a normal immune balance may be the most effective means for preventing the development of glomerular disease.

ACKNOWLEDGMENT

The authors thank the following physicians for providing data on glomerular disease patterns in their respective countries: Dr E. Kasamatsu (Paraguay), Dr N. Mazzuchi (Uruguay), and Dr A. Pinto (Venezuela).

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