The Current State of Poststreptococcal Glomerulonephritis

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ABSTRACT

Poststreptococcal glomerulonephritis is one of the oldest recognized renal diseases. In the past three decades, significant changes have occurred in its epidemiology, in new insight gained in the nephritogenic characteristics of streptococcal antigens, and in the natural history of the disease. The disease is now rare in industrialized nations, but in the underprivileged world, the burden of poststreptococcal glomerulonephritis ranges between 9.5 and 28.5 new cases per 100,000 individuals per year. Prophylactic antibiotic treatment is advisable in epidemic conditions and to household contacts of index cases in communities where the prevalence of the disease is high. The long-term prognosis is variable; in general, prognosis is excellent in children but significantly worse when it occurs in elderly individuals and in populations that present other risk factors of chronic kidney disease. Contemporary large-scale research strategies such as genome-wide sequencing may uncover new information about pathogenic factors contributing to disease.


One of the oldest clinical observations in nephrology is that “dropsy that follows scarlet fever” is associated with dark and scanty urine.1 The seminal contribution of von Pirquet2 attributed the disease to an antigen–antibody reaction that causes renal disease and was followed by investigations that vastly expanded our knowledge of the pathophysiology of immune complex–mediated inflammation and attempts to define the specific characteristics of streptococcal strains capable of causing nephritis.3 Here we address the changing epidemiology of poststreptococcal glomerulonephritis (PSGN), summarize guidelines for treatment of streptococcal infections from the standpoint of prevention of glomerulonephritis, and update the long-term prognosis of PSGN.

CHANGING EPIDEMIOLOGY OF ACUTE PSGN

It is widely acknowledged that the incidence of PSGN has decreased in the past three decades, but the present-day global burden of the disease is difficult to establish. This nephritis has practically disappeared in central Europe,4 where it is now more frequent in the elderly, especially in association with debilitating conditions such as alcoholism or intravenous drug use.5 In the Italian Biopsy Registry, PSGN is now more common after the age of 60 (0.9 patients per million) than before this age (0.4 patients per million), and in children younger than 15 yr, the incidence went from 2.6 to 3.7% of all primary glomerulopathies in the period 1987 through 1992 to only nine cases in the period 1992 through 1994.6 In China7 and Singapore,8 a reduction in the incidence of PSGN has been noted in the past 40 yr. In Chile, the disease has practically disappeared since 1999,9 and in Maracaibo, Venezuela, sporadic PSGN decreased from 90 to 110 cases per year in 1980 through 198510 to 15 cases per year in 2001 through 2005. In Guadalajara, México, the combined data from two hospitals showed a reduction in cases of PSGN from 27 in 1992 to only six in 2003 (García G, Arevalo A, Salazar AL, Ramírez S, Pérez G, Hospital Civil, Guadalajara, Mexico, personal communication, March 29, 2004). Similar reductions have been reported in Memphis, TN, where the incidence dropped from 31 patients per year in 1961 through 1970 to only 9.5 patients per year in 1979 through 1988.11

Nevertheless, PSGN remains a common disease in many rural and Aboriginal communities with low socioeconomic status. Such is the case in Australia12 and in Valencia, Venezuela, where the disease causes 70% of the hospital admissions in a pediatric nephrology service.13 In India, postinfectious glomerulonephritis represent 73% of the acute glomerulonephridities affecting the elderly,14 which may or may not rep-
resent a shift in age predominance such as has been referred to previously for Central Europe. 9

Despite the reduction in worldwide incidence of PSGN, epidemics and clusters of cases of PSGN continue to appear. Table 1 lists epidemics with >100 cases10,15–24 and Table 2 the epidemics with <100 cases or clusters in families or communities.9,25–42 Figure 1 shows that in the past 30 yr, large epidemics have been reported in countries in the middle range of the Human Development Index (HDI; between the 48th and the 87th rank place out of 177) and clusters of cases in countries in the upper 10% of the HDI.43 The countries where PSGN has not been reported in the past 30 yr are in the so-called “low” range of the HDI (0.449 to 0.336),43 and overwhelming social and health problems in combination with poor documentation resources (Figure 1A) are likely reasons for the apparent absence of PSGN.

In the past 30 yr, most of the smaller epidemics and clusters of cases are reported from poor communities, rural and/or Aboriginal, within countries in the upper 10% range of the HDI (Figure 1B). In these countries, the annual per capita health expenditure is nearly 5 times higher than that in countries where large epidemics are reported (Figure 1A) and is likely that the more efficient and better funded public health system in these nations facilitates the recognition and early antibiotic treatment of streptococcal infections in index cases of PSGN. Similarly, underprivileged communities in less developed nations may also have clusters of cases of acute PSGN that go unreported. The data reviewed here suggest that PSGN remains a significant health problem in underdeveloped countries. Additional insight into the potential burden of PSGN in these nations may be gained from the evaluation of the incidence of the most severe cases of the disease in pediatric referral hospitals. Acute postinfectious glomerulonephritis is frequently the cause of severe acute renal failure (requiring dialysis and/or admission to pediatric intensive care units) in underdeveloped countries. The proportion of cases of acute renal failure that correspond to acute postinfectious glomerulonephritis of demonstrated or assumed poststreptococcal etiology is 13% in New Delhi,44 30% in Istanbul,45 51.6% in Casablanca,46 4.6% in Lagos,47 27% in Bombay,48 19.2% in Lucknow,49 33% in Asunción,50 17.4% in Chandigarth,51 5.2% in Lima,52 and/or Aboriginal, within countries in the upper 10% range of the HDI (0.449 to 0.336),43 and overwhelming social and health problems in combination with poor documentation resources (Figure 1A) are likely reasons for the apparent absence of PSGN.

Table 1. Epidemics of acute PSGN with more than 100 cases

<table>
<thead>
<tr>
<th>Year</th>
<th>Location</th>
<th>Population Affected</th>
<th>Site of Infection</th>
<th>No. of Cases</th>
<th>Streptococcal Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1951 to 1952</td>
<td>Bainbridge, MD</td>
<td>Military recruits</td>
<td>Throat</td>
<td>180</td>
<td>M12</td>
</tr>
<tr>
<td>1964 to 1965</td>
<td>San Fernando, Trinidad, West Indies</td>
<td>Rural and city</td>
<td>Skin</td>
<td>760</td>
<td>M55, M49</td>
</tr>
<tr>
<td>1968</td>
<td>Maracaibo, Venezuela</td>
<td>Urban</td>
<td>Throat</td>
<td>384</td>
<td>ND</td>
</tr>
<tr>
<td>1967 to 1968</td>
<td>San Fernando, Trinidad, West Indies</td>
<td>Rural and urban</td>
<td>Skin</td>
<td>540</td>
<td>M49, M60</td>
</tr>
<tr>
<td>1974</td>
<td>Maracaibo, Venezuela</td>
<td>Urban</td>
<td>Skin</td>
<td>200</td>
<td>ND</td>
</tr>
<tr>
<td>1974</td>
<td>Baracoa, Guantánamo, Cuba</td>
<td>Rural</td>
<td>Skin and throat</td>
<td>295</td>
<td>ND</td>
</tr>
<tr>
<td>1986</td>
<td>San Fernando, Trinidad, West Indies</td>
<td>Rural and urban</td>
<td>Skin</td>
<td>181</td>
<td>M73, M48, M55, M57, 59</td>
</tr>
<tr>
<td>1995</td>
<td>Yerevan, Armenia</td>
<td>Urban and rural</td>
<td>Throat</td>
<td>196</td>
<td>ND</td>
</tr>
<tr>
<td>1995</td>
<td>San José, Costa Rica</td>
<td>Urban and Rural</td>
<td>Skin and throat</td>
<td>103</td>
<td>ND</td>
</tr>
<tr>
<td>1995</td>
<td>Vilnius, Lithuania</td>
<td>Urban and Rural</td>
<td>Skin and Throat</td>
<td>83 cases per 100,000 children</td>
<td>ND</td>
</tr>
<tr>
<td>1998</td>
<td>Nova Serrana, Minas Gerais, Brazil</td>
<td>Rural</td>
<td>Unpasteurized milk</td>
<td>135</td>
<td>S. zooepidemicus</td>
</tr>
<tr>
<td>1998 to 2001</td>
<td>Lima, Peru</td>
<td>Urban</td>
<td>Throat</td>
<td>186 (in clusters)</td>
<td>ND</td>
</tr>
</tbody>
</table>

aEpidemics with more than 100 cases of PSGN; data updated from reference42. ND, not determined.

bR. Lou, FUNDANIER, Guatemala City, Guatemala, personal communication, 2007.

cArticle was in Lithuanian, and we were not able to define the total number of cases.

dThe abstract cited does not permit definition of a specific epidemic peak.

GLOBAL BURDEN OF ACUTE PSGN

Carapetis et al.55 using 11 population studies reporting the incidence of acute PSGN, evaluated the global burden of PSGN. In children from less developed countries and minority populations, they found that the median incidence of disease was 24.3 cases per 100,000 person-years. In people older than 15 yr in these same countries, they estimated the incidence to be two cases per 100,000 person-years, basing their calculations on data from Kuwait. In more developed countries, the incidence was estimated at 0.3 cases per 100,000 person-years on the basis of the Italian Biopsy Registry. The global incidence of acute PSGN was estimated at 472,000 cases per year, 456,000 of which occurred in less developed countries.

Estimations of the global burden of PSGN may also be approached by considering that cases of PSGN with severe acute renal failure, usually as a result of a rapidly progressive course and crescentic glomerulonephritis, represent <1% of the total number of cases.56 These cases
derive from reports of pediatric acute renal failure from underdeveloped countries. In this study, the following assumptions were made: The patients with acute glomerulonephritis represented cases of PSGN. This was explicitly stated in most series but not in all of them; the cases listed had severe renal failure because they were seen at a referral hospital and admitted to intensive care units if the facility was available, and most underwent dialysis; and the total number of cases of acute PSGN in the general population was estimated assuming that uncomplicated cases were 100 (low estimate) to 300 (high estimate) more than life-threatening disease. The calculations are shown in Tables 3 and 4. Table 3 shows the selected series of acute renal failure used for analysis, the populations from which the cases were assumed to originate and the calculated high and low incidences of uncomplicated PSGN. In these calculations, 2850 (low estimate) to 8550 (high estimate) cases of PSGN occur annually in a total population of 29,967,989 inhabitants. It should be noted that three of the seven series used in these calculations are from India, one from Morocco, one from one from Thailand, and two from Nigeria; nevertheless, if these data are representative of the underdeveloped world, then it may be concluded that outside the industrialized countries, the annual incidence of PSGN is 9.5 to 28.5 new cases per 100,000 population of all ages (Table 4). Probably even the high estimate is an underestimation because underreporting of severe PSGN cases is likely as a result of local conditions and scarcity of pediatric nephrologists and because the cases in the adult population (arguably 10% of the total) are not taken into account. The low value is remarkably close to the value obtained by Carapetis et al. using population studies (Table 4). The high value exceeds the value given by Carapetis et al. by three-fold, but these authors acknowledge that their calculations were aimed to underestimate the global burden of the disease and that the true burden of PSGN was likely to be several-fold higher.

### NEPHRITOCENIC ANTIGENS

Group A streptococci are assumed the only strain capable of causing glomerulonephritis. Group C streptococci, however, have caused recent epidemics of PSGN, specifically *S. zooepidemicus* (Ta-
Table 3. Estimation of the burden of PSGN in underdeveloped countries on the basis of selected series of severe acute renal failurea

<table>
<thead>
<tr>
<th>City, Country</th>
<th>Population</th>
<th>Period of Study (yr)</th>
<th>ARF Total (n)</th>
<th>PSGN with Severe ARF (n)</th>
<th>APSGNb with Severe ARF per Year</th>
<th>Estimated Annual Incidence of Uncomplicated PSGN in General Populationc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casablanca, Morocco46</td>
<td>3,100,000</td>
<td>10</td>
<td>89</td>
<td>46</td>
<td>4.6</td>
<td>460 to 1380</td>
</tr>
<tr>
<td>Bombay, India48</td>
<td>12,500,000</td>
<td>2</td>
<td>48</td>
<td>13</td>
<td>6.5</td>
<td>650 to 1950</td>
</tr>
<tr>
<td>Lucknow, India49</td>
<td>2,541,101</td>
<td>3</td>
<td>52</td>
<td>9</td>
<td>3.0</td>
<td>300 to 900</td>
</tr>
<tr>
<td>Varanasi, India53</td>
<td>1,371,749</td>
<td>16</td>
<td>891</td>
<td>83</td>
<td>5.2</td>
<td>520 to 1560</td>
</tr>
<tr>
<td>Port Harcourt, Nigeria57</td>
<td>1,000,000</td>
<td>9</td>
<td>211</td>
<td>29</td>
<td>3.2</td>
<td>320 to 960</td>
</tr>
<tr>
<td>South Provinces, Thailand58</td>
<td>8,296,996</td>
<td>4 (2000 to 2004)</td>
<td>109</td>
<td>20</td>
<td>5.0</td>
<td>500 to 1500</td>
</tr>
<tr>
<td>Osun State, Nigeria54</td>
<td>2,158,143</td>
<td>9</td>
<td>123</td>
<td>9</td>
<td>1.0</td>
<td>100 to 300</td>
</tr>
<tr>
<td>Total</td>
<td>29,967,989</td>
<td></td>
<td></td>
<td></td>
<td>28.5</td>
<td>2850 to 8550</td>
</tr>
</tbody>
</table>

aThe population of the Mumbai metropolitan region of Bombay was obtained from http://theory.tifr.res.in/bombay/stats/pop; the population of Osun State, Nigeria, was obtained from http://www.onlinenigeria.com; and the population of the rest of the cities and the sum of the 14 provinces of Southern Thailand regions were obtained from http://en.wikipedia.org. APSGN, acute PSGN; ARF, acute renal failure.

bRequired admission to a referral hospital, intensive care unit, and/or dialysis.

cThis study assumed that proportion of cases of PSGN with severe ARF is <1% of the total number of uncomplicated symptomatic cases (see text), and estimates were made assuming that the total number of PSGN cases is 100 (low estimate) to 300 (high estimate) more than cases requiring intensive care and dialysis.

Table 4. Burden of APSGN in underdeveloped countries: Comparison with estimates made using population studiesa

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Estimated Annual No. of Cases of APSGN</th>
<th>Estimated Annual Incidence (Cases per 100,000 Population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carapetis et al.55</td>
<td>4,876,709,000</td>
<td>456,000</td>
<td>9.3</td>
</tr>
<tr>
<td>This studyb</td>
<td>29,967,989</td>
<td>2850 to 8550</td>
<td>9.5 to 28.5</td>
</tr>
</tbody>
</table>

aEstimations made by Carapetis et al.55 derived from the evaluation of 11 population studies.

bThis study assumed that proportion of cases of PSGN with severe acute renal failure is <1% of the total number of uncomplicated symptomatic cases (see text) and estimates were made assuming that the total number of PSGN cases is 100 (low estimate) to 300 (high estimate) more than cases requiring intensive care and dialysis.

Two antigens are actively investigated at the present time as the potential cause(s) of PSGN: The nephritis-associated plasmin receptor (NAPlr), identified as glyceraldehyde-3-phosphate dehydrogenase,63 and a cationic cysteine proteinase known as streptococcal pyrogenic exotoxin B (SPEB) that is generated by proteolysis of a zymogen precursor (zSPEB).61–63 Both of these fractions are capable of activating the alternate pathway of the complement system.3

NAPlr deposits are present in early biopsies of acute PSGN, and NAPlr antibody levels are detected by Western blot in convalescent sera of 92% of the patients with PSGN and 60% of uncomplicated streptococcal infections in Japan.59 Because NAPlr is co-localized with plasmin but not with complement or IgG, nephritogenicity is related to plasmin-binding capacity, which facilitates immune complex deposition and subsequent inflammation.60 More recent investigations by Fujino et al.64 demonstrated that the gene sequence and in vitro expression of NAPlr is not restricted to strains isolated from patients with PSGN and is also present in streptococci from groups A, C, and G.

SPEB/zSPEB is produced by nephritogenic streptococci from group A.65 Four independent studies (Oda and Yoshizawa, National Defense Medical College, Saitama, Japan, personal communication, December 27, 2007, see last paragraph of this section)62,63,66 showed that SPEB/zSPEB is deposited in biopsies of patients with acute PSGN and that high antibody titers to this antigen are present in convalescent sera of the vast majority of patients sampled in Latin America.62 Subsequent studies66 evaluated both NAPlr and SPEB in serum and biopsies obtained from patients in Venezuela, Chile, and Switzerland and detected SPEB deposits in 12 of 17 biopsies and serum anti-SPEB antibodies in 53 of 53 sera. In contrast, in the same material, circulating antibodies to NAPlr were found in only five of 47 sera and definite glomerular deposits in only one biopsy. SPEB co-localizes with complement deposits and within subepithelial electron-dense deposits (humps) that are the typical signature of acute PSGN. Thus far, this represents the only demonstration of a putative nephritogenic antigen inside the humps and suggests this localization was facilitated by the cationic, antigenic charge of SPEB, as postulated in previous studies.67,68

The contrasting results in antibody response and renal deposits of NAPlr and SPEB in patients from Japan and patients elsewhere suggest there may be more than a single streptococcal antigen responsible for glomerulonephritis, and different antigenic fractions could be nephritogenic in populations of different genetic background. In support of this conclusion are studies (see last paragraph of this article) demonstrating the absence of the gene encoding SPEB in the S. zooepidemicus responsible for the recent epidemic of glomerulonephritis in Brazil.23 Studying this same strepto-
coccal strain, Nicholson et al. found the gene encoding Szp5058 M-protein and showed that 33 of 44 patients were seropositive for the Szp5058 fusion protein. These authors noted that antiphagocytic properties of Szp proteins may be relevant in the pathogenesis of glomerulonephritis.

Both SPEB and NAPiR are capable of inducing chemotactic (monocyte chemotactant protein 1) and IL-6 moieties in mesangial cells, promoting enhanced expression of adhesion molecules. Recent investigations also demonstrated peripheral blood leukocytes respond with release of IL-6, TNF-α, IL-8, and TGF-β when reacted with SPEB. These findings underline the inflammatory potential of these putative nephritogens.

The role of plasmin-binding activity in the pathogenesis of PSGN is an attractive possibility. The plasmin-binding activity of both NAPiR and SPEB is widely recognized. Similar properties are present in streptokinase and enolase, and the nephritogenic potential of the latter is based on its plasmin-binding properties. Recent investigations by Oda and co-workers (National Defense Medical College, Saitama, Japan, personal communication, December 27, 2007) demonstrated by double-staining method that NAPiR and SPEB both are localized in the glomerular mesangium of biopsies of patients with acute PSGN (Figure 2) and because they found similar localization of both antigens postulated that plasmin-binding activity may be a common nephritogenic characteristic in both antigens.

**TREATMENT GUIDELINES FOR STREPTOCOCCAL INFECTIONS WITH POTENTIAL FOR GLOMERULONEPHRITIS**

Acute PSGN is prevented by early antibiotic treatment, and the spread of nephritis-associated streptococcal infection is contained by prophylactic antibiotic treatment to individuals at risk. The challenge is to define who should be treated when the diagnosis of streptococcal infection is uncertain and when prophylactic treatment of a given population is warranted. The decision is straightforward with active skin infections because the differential diagnosis is between staphylococcal and streptococcal impetigo, and both should be treated with penicillin except when methicillin-resistant staphylococci are prevalent in the community.

In contrast, the diagnosis of streptococcal pharyngitis on clinical grounds alone is uncertain, and only 10 to 20% of the patients who present with a sore throat in general clinical practice have a positive culture for group A Streptococcus. Because clinical judgment may miss half of the streptococcal pharyngitis and wrongly identify as such 20 to 40% of the cases of sore throats, several clinical scoring systems have been developed to increase the accuracy of diagnosis for the prescription of antibiotics. Among the most popular are the scores proposed by Centor et al. and McIsaac et al. that have a range from 0 to 4 and incorporate age as a risk factor. The McIsaac score gives 1 point each to the following criteria: Temperature >38°C, no cough, tender anterior cervical adenopathy, tonsilar swelling or exudates, and age between 3 and 14 yr. Age 15 to 44 yr gets +1 point. Using this scoring system, the sensitivity and specificity of the diagnosis are 85 and 92%, respectively; and in practical terms, antibiotic treatment is recommended on clinical grounds alone when the score is 4, antibiotic treatment is not recommended (and culture is unnecessary) when the score is 0 or 1, and cultures should be obtained and treatment given only when the result is positive when score is 2 or 3. Rapid tests for streptococcal antigen detection suitable for office practice have been developed and may be used as a confirmatory test for children with tonsillar exudate and no cough, but their sensitivity is too low to support use without culture confirmation of negative results.

Patients with acute PSGN should be treated as though they have active streptococcal infection. The reason for this recommendation is that positive cultures may sometimes be obtained from patients in whom upper respiratory or skin infections are not clinically evident. Treatment of a carrier state may prevent spread to other household members; in addition, at least one report suggested that patients who receive PSGN antibiotic treatment have a milder clinical course.

Prophylactic penicillin treatment should be used in epidemics in closed communities and prescribed to household contacts of index cases in areas where PSGN is very common or when clusters of cases are reported. This recommendation is based on the finding that cross-infection among family members of index cases in communities where PSGN is prevalent is very high. In Maracaibo, 95% of the siblings and 79% of the parents of index cases presented serologic evidence of recent streptococcal infection. Studies of Australian Aboriginal communities also supported this notion. Johnston et al. found treatment with benzathine penicillin G targeted to children with skin sores and household contacts of index cases prevented new cases of acute PSGN, in contrast with the
incidence in communities in which no intervention was attempted.

**PROGNOSIS OF PSGN**

The immediate prognosis of acute PSGN is excellent for children. In contrast, elderly patients who develop acute PSGN usually present with debilitating conditions (malnutrition, alcoholism, diabetes, or chronic illness) and have a high incidence of azotemia (60%), congestive heart failure (40%), and proteinuria in the nephrotic range (20%). Death may occur in as many as 20 to 25% of these patients.84,85

The long-term prognosis of PSGN in children has been the subject of many studies. The initial reports of natural history of PSGN in the first half of the 20th century indicated an excellent prognosis, but follow-up periods were relatively short. Subsequent studies gave conflicting results because abnormal urinary findings were as low as 3.5%86 and as high as 60%.87

Table 5 summarizes the results of several studies published before the year 2000 with 5 to 18 yr of follow-up.86–93 These pooled data, of course, come from studies with dissimilar methods and widely different results and therefore is presented only as a rough approximation of what to expect in the long-term natural history of PSGN. Table 6 shows data from the three studies reported after 2000.94–96 When all studies reporting children followed for 10 to 20 yr after acute PSGN are taken into account, approximately 20% of the patients have abnormal urine analyses, but the incidence of azotemia is <1%. Our own data** include 110 children followed for 15 to 18 yr after the acute episode PSGN and show an incidence of 7.2% for non-nephrotic proteinuria, 5.4% for microhematuria, 3.0% for hypertension, and 0.9% for azotemia. A particularly bad prognosis was reported for patients from a recent epidemic in Minas Gerais (Brazil), a majority of which were adults (Table 6). Chronic renal failure developed in 8% of these patients after 5 yr.95 Carefully collected data in Aboriginal communities in the Northern Territory of Australia indicated that PSGN is associated with an increased risk for albuminuria (adjusted OR 6.1%; 95% confidence interval 2.2 to 16.9) and hematuria (OR 3.7; 95% confidence interval 1.8 to 8.0) in relation to control subjects who did not have PSGN.96

From the previous discussion, it follows that, in general, chronic renal failure resulting from PSGN is exceptional but specific groups of patients do not share this favorable outlook. A group of patients with especially poor long-term prognosis are elderly patients who develop persistent proteinuria in the nephrotic range; 77% of these patients develop chronic renal failure.97 For children, the prognosis of PSGN may be significantly worse in specific communities in which other risk factors for chronic renal failure are common. This is the case in Australian Aboriginal communities, where low birth weight (resulting in the endowment of a low nephron number), diabetes, and metabolic syndrome are prevalent. White et al.96 postulated that PSGN may represent an additional risk factor that would explain why the incidence of ESRD is several-fold higher in these communities than in the non-Aboriginal population.98,99

**PRESENT AND FUTURE ROLE OF STREPTOCOCCAL GENOMICS IN PSGN**

In the past 8 yr, application of genome-wide investigative strategies to unsolved problems with group A *Streptococcus* has contributed significant new information about molecular events occurring during host–pathogen interactions.100–102 These new techniques include, among others, bacterial genome sequencing, expression microarray (transcriptome) analysis, comparative genomics by DNA-DNA microarray analysis, and proteomics.99 For example, we now have genome sequences available for 11 strains of group A *Streptococcus* recovered from diverse types of infection, making this organism one of the most extensively characterized of any human bacterial pathogen.103 This remarkable array of new information gives new insight into the pathogenesis of

Table 5. Long-term prognosis of PSGN: Summary of series published before 2000 with 5 to 18 yr of follow-up

<table>
<thead>
<tr>
<th>Findings</th>
<th>% of Patients</th>
<th>Patients with Positive Finding/Total Patients Followed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any abnormality</td>
<td>17.4</td>
<td>174/998</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>13.8</td>
<td>137/997</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13.8</td>
<td>137/998</td>
</tr>
<tr>
<td>Azotemia</td>
<td>1.3</td>
<td>14/1032</td>
</tr>
</tbody>
</table>

*Data correspond to pooled patients from the studies cited in the text.86–93*

Table 6. Long-term prognosis of PSGN: Summary of series published after 2000

<table>
<thead>
<tr>
<th>Location</th>
<th>No. of Patients Followed (Population)</th>
<th>Follow-up (yr)</th>
<th>Albuminuria (%)</th>
<th>Hematuria (%)</th>
<th>Hypertension (%)</th>
<th>Decreased Renal Function (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maracaibo, Venezuela94</td>
<td>110 (urban and rural)</td>
<td>15 to 18</td>
<td>7.2</td>
<td>5.4</td>
<td>13.7</td>
<td>Increased Scr in 0.9% of the patients</td>
</tr>
<tr>
<td>Northern Territory, Australia95</td>
<td>63 (rural)</td>
<td>&gt;13</td>
<td>13 (controls 4%)</td>
<td>21 (controls 7%)</td>
<td>Not different from controls</td>
<td>Not different from controls</td>
</tr>
<tr>
<td>Minas Gerais, Brazil97</td>
<td>56 (rural)</td>
<td>5</td>
<td>8</td>
<td></td>
<td>30</td>
<td>8% (Ccr &lt; 60 ml/min)</td>
</tr>
</tbody>
</table>

*Ccr, creatinine clearance; Scr, serum creatinine.*
pharyngitis, acute rheumatic fever, puerperal sepsis, and other invasive infections and has allowed identification of vaccine targets, however, notably absent has been the application of these new techniques to problems in PSGN.

As a consequence, one of us (J.M.M.) recently began a molecular genomics initiative designed to contribute new information about the pathogenesis of PSGN, aimed at providing new leads for subsequent clinical and translational research. One of the first goals has been to sequence the genome of streptococcal strains causing or repeatedly associated with PSGN (so-called “nephritogenic” strains) and compare their genetic makeup with the genome of strains not associated with PSGN (“non-nephritogenic” strains). Using this approach, Beres et al. found considerable genetic differences in nephritogenic and non-nephritogenic strains of serotype M12 Streptococcus. For example, the nephritogenic strain had a large segment of DNA, referred to as region of difference 2 (RD.2), that was lacking in the non-nephritogenic strain. RD.2 encodes a large, predicted, exported protein that is not made by other sequenced group A Streptococcus strains and thus warrants further investigation in the context of PSGN pathogenesis. More recently, as noted, we have sequenced the genome of a strain of S. zooepidemicus causing a large nephritis outbreak after the ingestion of unpasteurized milk from cows with mastitis. Unexpected, the gene encoding SPEB, one of the secreted bacterial products that contribute to the survival of Streptococcus in saliva, was absent. Further analysis of the genomic sequence revealed that a large block of DNA encoding SPEB present in all group A Streptococcus strains studied to date is missing in this strain, perhaps as a result of a deletion event (unpublished data). This finding is important because SPEB has been implicated in the pathogenesis of PSGN (see the Nephritogenic Antigens section), and the genomic data clearly indicate that if it participates, then it cannot be the sole causative molecule in all patients. Molecular proteogenomics are also at the crossroads of a paradigm shift in vaccine research toward the strategy of “reverse vaccinology.” This strategy consists of using a complete genomic sequence to identify large numbers of potentially protective antigens, expressing them in a recombinant form, and then testing them with a battery of immunologic assays. These powerful new tools perhaps coupled with renewed interest in nonhuman primate models of streptococcal infection are likely to usher a new era of the study of PSGN.

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DISCLOSURES

None.

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