ACUTE RHEUMATIC FEVER

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To many, the very title of this article seems quaint, as it seems to conjure up another era. Indeed, Dr. Robert Quinn, Professor Emeritus of Preventive Medicine at Vanderbilt, wrote on the subject in 1989 (1), and his article, covering data through about 1988, is written in an almost historical tone, as if he were recording the end of a disease. As shown in Figure 1, the decline in incidence of rheumatic fever (RF), which started around the turn of the century, has continued dramatically since World War II, and there were only 147 cases reported in the U.S. in 1986, as opposed to over 10,000 in 1961. This nearly 100-fold decline over 25 years appeared to predict the virtual elimination of the disease in this country over the next few years.

That the disease has not been eliminated, however, was illustrated dramatically over the past few years by several large outbreaks, notably in Salt Lake City (2), Akron (3), San Diego (4), Columbus (5), Pittsburgh (6) and Nashville (7), among others. Because the Nashville experience is illustrative of several of the other outbreaks, and because I have some firsthand knowledge of those cases, I would like to describe them in some detail.

The Nashville Outbreak

Like most hospitals in the U.S. Vanderbilt Hospital had shown a steady decline in cases of RF, at least since 1970 (Fig. 2). The 26 cases over a 2 year period represented an approximate fourfold increase over the incidence of the previous few years. It should be pointed out, incidentally, that these were limited to the pediatric inpatient service. It does not include adults or nonhospitalized people with "post-streptococcal arthritis."

As in other recent outbreaks, the demographics of the Nashville cases were also unpredicted. Whereas RF has traditionally been the province of the poor, for the most part (Fig. 3), the Nashville patients were fairly representative of the community at large, with a largely urban, middle class population. As shown in Table 1, 80% were white, and most were well above the poverty line. Although the family size was slightly larger

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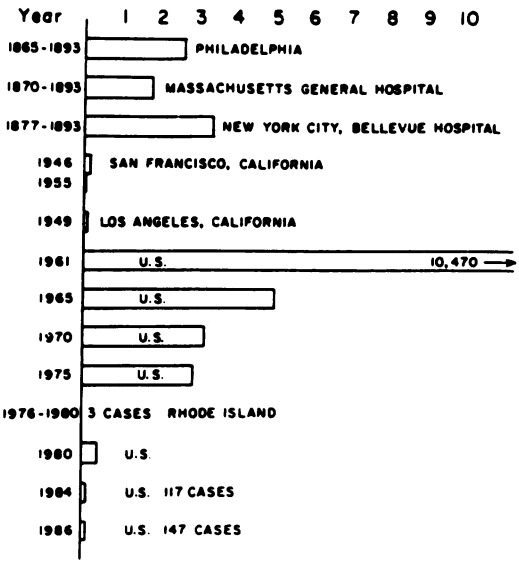

FIG. 1. Incidence of rheumatic fever in selected localities and in the United States (× 1000) (Ref. 1, reprinted with permission).

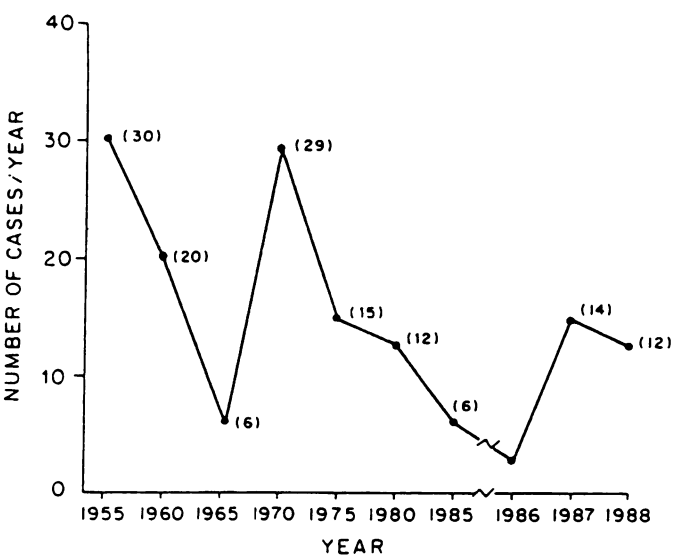

FIG. 2. Rheumatic fever in Vanderbilt Children's Hospital 1955–88. (Ref. 7, reprinted with permission).

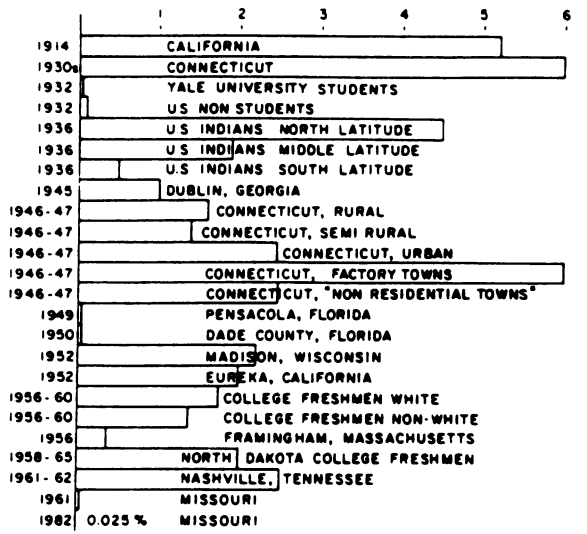

FIG. 3. Demographics of rheumatic fever in the U.S. (× 1000) (Ref. 1, reprinted with permission).

TABLE 1
Nashville Epidemic of ARF—1987–88 Demographics (Ref. 7)

No. Patients	26
Age	4–14 (Mean 9.8)
Race	80% white (expected)
Family size	4.5 (3.2 expected)
Crowding	1.6/bedroom (0.97 expected)
Residence	80% urban (60% expected)
Median income	$18,000
Below poverty line	19% (9.2% expected)

than predicted, overcrowding did not seem to be an important factor either.

Clinically, the most frequent major criterion for RF was, surprisingly, carditis, with arthritis and chorea also frequent (Table 2). As in other recent epidemics, nodules were not seen. Typically, about 60% had a history of recent pharyngitis, but only 1 had received benzathine penicillin.

When Nashville is compared to several other recent outbreaks (Table 3), the incidence of both carditis and chorea was higher than in most other cities, but there was considerable variation. If one combines the 5 outbreaks shown in Table 3, there were 180 cases of RF reported, with 60% of the cases overall having carditis and 56% with arthritis.

TABLE 2
Nashville Epidemic of ARF 1987–88 Clinical Data (Ref. 7)

Carditis	72%	Pharyngitis 15/26
Arthritis	58%	Antibiotics 7/26
Chorea	31%	(1 benzathine penicillin)
Rash	4%	Pos. throat culture 12/26
Nodules	0	Positive ASO 100%

TABLE 3
Recent ARF Outbreaks

	Salt Lake City	Columbus	Akron	Pittsburgh	Nashville
# Cases	74	40	23	17	26
Manifestations					
Carditis	72%	50%	30%	59%	73%
Arthritis	46%	65%	78%	47%	58%
Chorea	31%	18%	9%	30%	31%
Reference	2	5	3	6	7

As stated above, the demographics of the Nashville cases show a pattern atypical from the pattern of several decades ago, when RF was strongly correlated with poverty and overcrowding. This is shown most dramatically in the Salt Lake City epidemic, where the patients were 96% white, with a mean family income of $24,000 to $34,000 (2). However, the one constant over the years remains, as was shown in Nashville, was the inadequate treatment of the prior streptococcal infection. I will have more to say about that later.

Rheumatic Fever in Adults

With the exception of the virtual disappearance of nodules and a probable decrease in erythema marginatum, the Jones criteria are still applicable in the pediatric age group (8). In adults, however, they are much less useful. This was pointed out dramatically by Barnert et al 15 years ago (9). As shown in Table 4, these authors reported 53 adults from the San Antonio area. In this epidemic, by far the most frequent clinical manifestations of RF were arthritis and fever. Few met the Jones criteria for diagnosis of RF. Interestingly, of the 8 patients with carditis, only 2 had persistent valvular abnormalities, and one of these had prior rheumatic valvular heart disease.

The relative lack of utility of the Jones criteria in adults was also demonstrated in a recent epidemic at the San Diego Naval Training Center (4). In this outbreak, 10 of 10 patients had arthritis and fever, and 3 had carditis. However, none had chorea or rash, and 1 had nodules.

TABLE 4
Rheumatic Fever in Adults (Ref. 9)

Major Criteria	
Polyarthritis	53/53 (100%)
Carditis	8/53 (15%)
E. Marginatum	2/53 (4%)
Chorea	0
Nodules	0
Minor Criteria	
Fever	48/53 (91%)
Increased ESR	53/53 (100%)
1° Heart block	15/53 (28%)
Previous RF	12/53 (23%)
Increased ASO	51/52 (98%)

Unlike the apparent change in the clinical manifestations of RF in children, the manifestations in adults have probably not changed much, since epidemics from the 1950's also showed a very low incidence of chorea, rash, and nodules in adults (10). Engleman et al reported in 1954 that the incidence of subsequent rheumatic heart disease after RF was 66–74% in children, 51% in adolescents, and 17–24% in adults (11).

Arthritis of Rheumatic Fever

As a rheumatologist, I feel compelled to comment briefly on the characteristics of the arthritis of RF. As shown in Fig. 4, the knee is the most common presenting joint in adults, and was eventually involved in nearly 100% of the San Antonio patients. Pope recently summarized the clinical manifestations of RF, and pointed out several important characteristics of the arthritis (12) (Table 5). The typical presentation, especially in adults, is the abrupt onset of a pauciarticular lower extremity large joint arthritis which may be migratory but is often additive.

Prevention of Rheumatic Fever

To prevent RF we need only return to the lesson learned over 4 decades ago: Rheumatic fever is preventable by the widespread use of benzathine penicillin. This is shown in Fig. 5, where the prophylactic use of benzathine penicillin in 1987 abruptly lowered the incidence of both streptococcal infection and RF in San Diego. It is even more dramatically shown in Fig. 6, where an entire country, Costa Rica, has markedly reduced its incidence of RF by the widespread use of benzathine penicillin to treat pharyngitis.

The reasons for the recent resurgence of RF are unclear, but a general relaxation of our formerly aggressive posture toward treatment of phar-

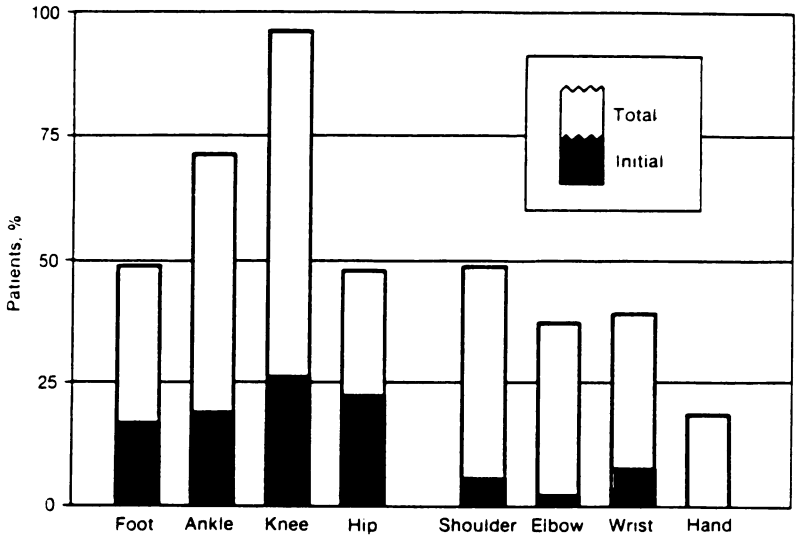

FIG. 4. Joint involvement in adult rheumatic fever (Ref. 9, reprinted with permission.)

TABLE 5
Arthritis of RF

Migratory (children)
Migratory and/or additive (adults)
Abrupt onset
Lower extremities predominate
Symptoms disproportionate to signs
Rapid response to salicylates (children)
Gradual response to salicylates (adults)

yngitis is probably the most important. Others have pointed out, however, that there has been a resurgence of some of the rheumatogenic strains of streptococci, including the highly mucoid M-type 18 (14).

Immunogenetics

Rheumatic fever is the classic example of an environmentally induced autoimmune disease in a genetically predisposed host. Table 6 shows some of the putative cross-reactive antibodies associated with various manifestations of RF. Of these, the best studied is the cross-reactivity between streptococcal cell membranes and cardiac sarcolemmal membranes. As shown by Zabriskie and his colleagues (15), virtually 100% of patients with RF have antimyocardial antibodies. Unlike similar anti-

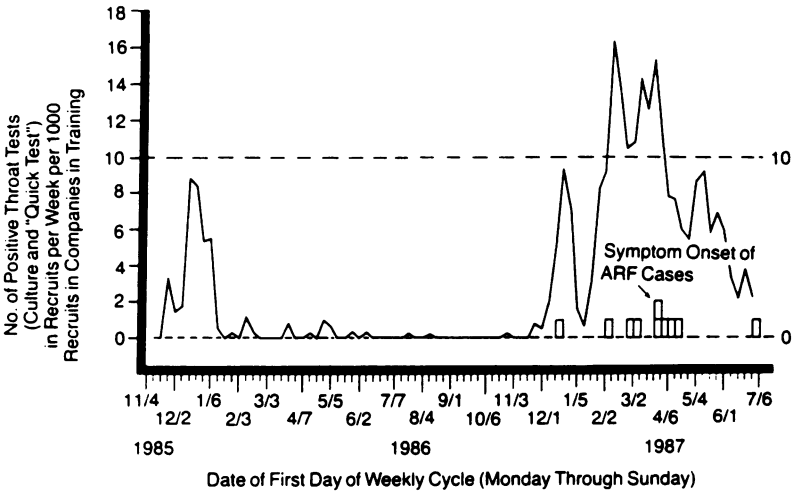

FIG. 5. The San Diego epidemic of rheumatic fever. Benzathine penicillin prophylaxis for all recruits was begun in 1987. (Ref. 4, reprinted with permission.)

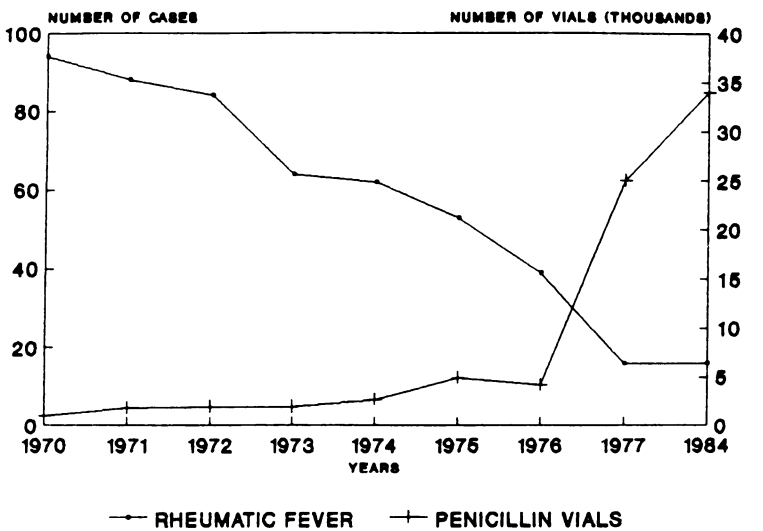

FIG. 6. Effect of benzathine penicillin usage on the incidence of rheumatic fever in Costa Rica (Ref. 13, reprinted with permission).

bodies produced following myocardial infarction, those in RF are completely absorbed by streptococcal cell membranes.

RF has been noted for years to aggregate in families, but the specific gene(s) responsible for susceptibility has remained elusive. Class 1 HLA

TABLE 6
Streptococcal Cross-reacting Antibodies (Ref. 15)

Strep. Antigen	Human Tissue	RF Manifestations
M-Protein	Sarcolemma	?
Cell Membrane	Sarcolemma	Carditis
Polysaccharide	Valve glycoprotein	Valvular disease
? Cell Membrane	Caudate nucleus	Chorea

antigen studies have been negative (16). Class II HLA-DR antigens have been associated with RF, but the specific antigen varies among the populations studied, implying that the actual antigen is not an HLA-DR antigen but one which is closely linked to the HLA-DR genes (17).

A possible breakthrough in our understanding of RF genetics may be at hand, however. In 1979 Patarroyo et al (18) described a lymphocyte antigen found in 100% of his Colombian patients with RF. This antigen has since been studied extensively by Gibofsky, Zabriskie and their associates (18), and a number of observations have been made. The antigen is a B cell alloantigen which is normally expressed on a small percentage of B cells but is found on a much higher percentage of cells of patients with RF. It is not an activation antigen, and about 10% of the healthy population express high levels of the antigen. Since roughly 90–100% of RF patients from a number of populations have expressed the antigen, it is their hypothesis that the healthy individuals with the antigen expressed represent the "at risk" population for developing RF.

SUMMARY AND CONCLUSIONS

A funny thing has happened on our way to the elimination of rheumatic fever from the United States. It is quite clear that, at least in some areas, rheumatic fever has made a dramatic resurgence. Although all the factors accounting for this are not clearly understood, there are several obvious conclusions that must be drawn:

1. Rheumatic fever is no longer the province of the poor and overcrowded.
2. Clinical manifestations, as embodied in the Jones criteria, may have changed somewhat over the years.
3. New insights into the genetics and immunology of rheumatic fever may lead to a vaccine and/or effective therapy in the future.
4. Rheumatic fever will continue to occur unless and until we resume an aggressive approach to the treatment and prophylaxis of pharyngitis, probably utilizing benzathine penicillin as our primary drug.

REFERENCES

1. Quinn RW: Comprehensive review of morbidity and mortality trends for rheumatic fever, streptococcal disease, and scarlet fever: the decline of rheumatic fever. *Rev of Inf Dis* 1989; 11(6): 928.
2. Veasy LG, Wiedmeier SE, Orsmond GS, et al. Resurgence of acute rheumatic fever in the intermountain area of the United States. *N Engl J Med* 1987; 316: 421.
3. Congeni B, Rizzo C, Congeni J, et al: Outbreak of rheumatic fever in northeast Ohio. *J Pediatr* 1987; 111: 176.
4. Wallace MR, Garst PD, Papadimos TJ, et al: The return of acute rheumatic fever in young adults. *JAMA* 1989; 262(18): 2557.
5. Hosier DM, Graenen JM, Teske DW, et al: Resurgence of acute rheumatic fever. *Ann J Dis Child* 1987; 141: 730.
6. Wald ER, Dashefsky B, Feidt C, et al: Acute rheumatic fever in Western Pennsylvania and the tristate area. *Pediatrics* 1987; 80: 371.
7. Westlake RM, Graham TP, Edwards KM: An outbreak of acute rheumatic fever in Tennessee. *Pediatr Infect Dis J* 1990; 9: 97.
8. Ad Hoc Committee to Revise Jones Criteria (Modified): Jones criteria (revised) for guidance in the diagnosis of rheumatic fever. *Circulation* 1984; 69: 204A.
9. Barnert AL, Terry EE, Persellin RH: Acute rheumatic fever in adults. *JAMA* 1975; 232(9): 925.
10. Adatto IJ, Poske RM, Pouget JM, et al: Rheumatic fever in the adult. *JAMA* 1965; 194: 141.
11. Engleman EP, Hollister LE, Kolb FO: Sequelae of rheumatic fever in men: 4 to 8 year follow-up study. *JAMA* 1954; 155: 1134.
12. Pope RM: Rheumatic fever in the 1980s. *Bull on the Rheum Dis* 1989; 38(3): 1.
13. Arguedas A, Mohs E: Prevention of rheumatic fever in Costa Rica. *J Pediatr* 1992; 121: 569.
14. Bisno AL: Group A streptococcal infections and acute rheumatic fever. *N Engl J Med* 1991; 325(11): 783.
15. Zabriskie JB: Rheumatic fever: the interplay between host, genetics, and microbe. *Circulation* 1985; 71(6): 1077.
16. Falk JA, Fleischman JL, Zabriskie JB, et al: A study of HLA antigen phenotype in rheumatic fever and rheumatic heart disease patients. *Tissue Antigens* 1973; 3: 173.
17. Ayoub EA, Barrett DJ, Maclaren NK, et al: Association of class II human histocompatibility leucocyte antigens with rheumatic fever. *J Clin Invest* 1986; 77: 2019.
18. Patarroyo ME, Winchester RJ, Vejerano A, et al: Association of a B-cell alloantigen with susceptibility to rheumatic fever. *Nature* 1979; 278: 173.
19. Gibofsky A, Khanna A, Suh E, et al: The genetics of rheumatic fever: relationship to streptococcal infection and autoimmune disease. *J Rheumatol* 1991; 18: 1.

DISCUSSION

Rich, Houston: Nice paper, John. There has been another kind of resurgent streptococcal disease since 1985, and that has been the occurrence of toxic shock-like syndrome. Has there been any correlation in outbreaks between this new virulence factor that appears to be associated with toxic shock-like syndrome and the appearance of acute rheumatic fever?

Sergent: Alan Bisno, whose work I quoted here, was in Nashville recently to give Grand Rounds and he was asked that exact same question. They seem to be totally different. They are both mucoid-producing streptococci, but the toxic shock syndrome does not seem to be related.

McCarty, Milwaukee: Excellent review. We have been seeing sporadic cases throughout

the last 10 years, maybe one or two a year. We have been calling them "post-Streptococcal" arthritis. I just saw a case last week. Do you have any data on the occurrence of sporadic cases? One tip-off to post-Streptococcal arthritis is the finding of an inflammatory-type fluid, that is lots of white cells with a polymorph-predominance but with a good mucin clot and high viscosity. It's an almost unique finding. It actually appears in Ropes and Bauer's monograph on joint fluid published in 1953.

Sergent: I agree with that observation. I don't know the incidence of sporadic rheumatic fever. Most of us diagnose it just as Dr. McCarty does because we don't want to stigmatize our patients from ever getting life insurance or whatever. So most of us call it, in adults, post-streptococcal arthritis and that seems to pass the insurance carriers. I don't know what the incidence of that disease is.

Woodward, Baltimore: That was a very nice paper. Do you have any crude rates of how many had a strep infection and did not develop rheumatic fever versus those who did?

Sergent: We don't have them at Nashville, but if you look at the San Diego Naval Base, it looks as though there are about 10 times as many strep infections as rheumatic fever, which you might expect, I suppose, if this B cell allo-antigen is the important factor.

Conti, Gainesville: John, I was sort of surprised by the high prevalence of carditis in your patients in the Nashville group. I wonder if that has something to do with the way you were identifying these patients with mitral regurgitation and aortic insufficiency. Did you use echo-Doppler techniques?

Sergent: Most of these children actually had clinical carditis that would have been diagnosed many years ago. The other childhood epidemics around the country had about the same incidence, 30–50%.

Sanford, Dallas: I enjoyed that very much. One of the confounding factors in the last several years has been the recognition that group C and group G streptococci, which are beta hemolytic, have been associated with pharyngitis, particularly in young adults. These two groups of streptococci also have streptolysin O, so you can see rises in antistreptococcal or antistroptolysin O titer without concomitant rises in anti-DNAase B titer. At least in some of the patients we have seen, this has confounded people considerably. I think that it is quite clear that both C and G streptococci are not associated with rheumatic fever.

Sergent: It's a very good point.

Williams, Gainesville: This is a very nice review. I have some hot data on this B cell antigen. John Zabriskie and I have been working on this for a number of years. We have now cloned this antigen and sequenced it. We have the complete amino acid sequence for the B cell antigen. It is a very strange protein. It has a helical structure and it has tremendous homology to tropomyosin and myosin, as well as streptococcal M protein. Why patients with rheumatic fever should have this strange B cell antigen up-regulated on their B cells is really still a mystery.

Sergent: Well, you can see that my point was correct. I knew that I was over my head with this topic.

Schreiner, Georgetown: You mentioned that there are familial clusters, which is an old observation and it's interesting that it is repeated. You didn't break down inside the rheumatic fever incidence the differences between polyarthritis and carditis. Did you have families in which the carditis was prominent? Did you have any crossover families in which the carditis existed in the same family where no carditis existed, or were they clustered in families separately?

Sergent: We actually had no familial clusters in our group in Nashville and the data weren't reported from the other series, so I can't answer that question. It's a very good question, but I don't know the answer.

Schreiner: The reason I ask is, just to open up your thinking, many years ago when we were doing complement receptor determinations by the old techniques, before monoclonal

antibodies, using coated sheep cells and rosette formation, we had a medical student who got hold of one surgical heart. He mapped the endothelium of the heart and a number of complement receptors in that particular heart clustered around the mitral and aortic valves, which was very interesting. There may be a genetic basis for the carditis that deals with the receptor populations independently of their susceptibility to streptococci.

Sergent: An interesting concept.