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SPECIAL ARTICLE

Current problems in managing streptococcal pharyngitis

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It is a pleasure for me to give the Third Annual Lewis W. Wannamaker Memorial Lecture. In my opinion, Lewis Wannamaker had the most brilliant career known in the study of the streptococcus. His accomplishments were legion; they varied from seminal epidemiologic studies to very important clinical observations to profound laboratory discoveries. He was recognized internationally. His greatest contribution, however, probably was to those of us who worked with and under him. He was an elegant model, both as a scientist and as a human being. He was my friend for 35 years, and I am privileged to honor him by giving this lecture in his memory.

The first Wannamaker lecture, by Markowitz, was entitled, "The Decline of Rheumatic Fever: Role of Medical Intervention"[1]; the second, by Parker, was entitled "Changing Concepts of Group A Streptococcal Disease over Four Decades" (unpublished). In his contribution to the earlier conference, entitled "The Management of Streptococcal Pharyngitis in an Era of Declining Incidence of Rheumatic Fever," Markowitz opened his presentation with an interesting concept.[2] He broke down the last 30 years into decades. From 1950 to 1960 was the decade of discovery; we learned that we could prevent first attacks of rheumatic fever but that we could not diagnose streptococcal pharyngitis very well without the use of a throat culture. There followed a decade that Markowitz called the decade of dissemination; the management of streptococcal infection and the widespread use of the throat culture seemed to be satisfying to physician and patient alike. The 1970s were the decade of dissonance; we learned that the throat culture could not distinguish carriers from infected patients, we became aware of treatment failures and the problems in their management, many began to question the cost benefit of the treatment of streptococcal infections, and above all, it appeared that rheumatic fever was being eliminated in the United States. For the first time since the early 1950s, we are having to rethink seriously the management of streptococcal infections. All of these things led to my decision to talk about what I construe to be problems in 1986.

I make no attempt to discuss all of the issues that are raised in the management of streptococcal pharyngitis. Instead, I have chosen five areas: the streptococcus carrier; the eradication by antimicrobials of streptococci from the tonsillar pharynx, the status of rapid diagnosis, the effect of treatment on the symptoms and signs of streptococcal pharyngitis, and other bacteria as causes of pharyngitis. I mention only briefly the cost effectiveness or cost benefit of treatment and the possibility that rheumatic fever is returning.

STREPTOCOCCUS CARRIER STATE

Streptococcus carriage is probably the most troublesome issue for both the researcher and the clinician. The

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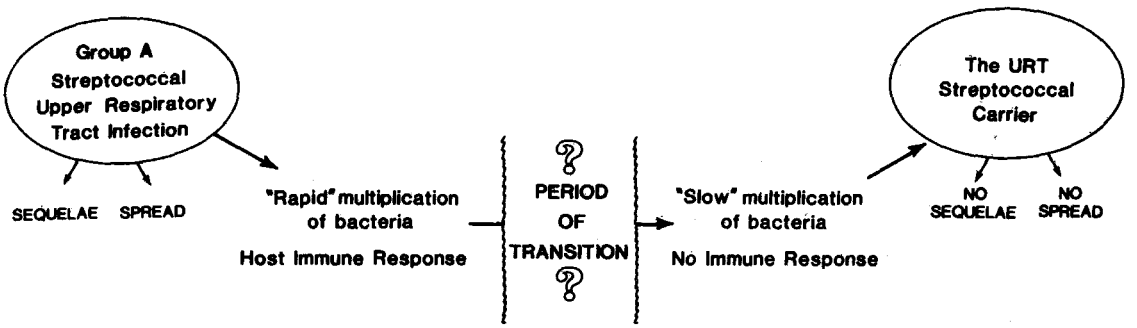

Fig. 1. Schematic representation of transition from bona fide streptococcal pharyngitis to streptococcal carrier state. *URT*, Upper respiratory tract. (From Kaplan EL. In Shulman ST, ed. Eighty-sixth Ross Conference on Pediatric Research. Columbus, Ohio: Ross Laboratories, 1984:92-100.)

most thoughtful work on this problem has come from Kaplan et al. in Minnesota.[3-5] A big problem is the definition of a carrier. We know that if a patient has a bona fide, untreated streptococcal infection, the organism can be cultured from the tonsillar pharynx for long periods of time. There is also good evidence that streptococci can be inhaled into the respiratory tract and remain there for a few hours or possibly a few days without causing prolonged carrier status or disease. What we really do not know is whether the streptococcus organism can be carried in the tonsillar pharynx for a long time without the host reacting with either symptomatic disease or an asymptomatic state accompanied by an antibody response. The clinical and epidemiologic consequences of the carrier state are also troublesome, as is its management.

Kaplan[6] attempted to elucidate these problems with a diagram (Fig. 1). Shortly after establishing itself in the pharynx, the group A streptococci can cause respiratory tract infections that may result in sequelae and spread readily to other individuals. The organism multiplies rapidly in the pharynx, and the host has an immune response. This is followed by a period of transition, after which the organism multiplies more slowly. There is no further immune response, and during that period of "carriage" of the organism, no sequelae and no spread occur.

This has led me then to outline what I have termed the correlates of streptococcal carriage: (1) The positivity of throat cultures decreases over time after initial infection. (2) The contagiousness of the infected host is related inversely to the duration of carriage. (3) Suppurative complications are more common with acute infection. (4) Probably most important, rheumatic fever occurs within 3 to 5 weeks after onset of a streptococcal infection; carriage after that time is less dangerous. These correlates are depicted graphically in Fig. 2. The data used in this figure were adapted from studies done by the Wyoming group, primarily Wannamaker[7] and Krause et al.[8] Although taken from different studies, I believe the observations are accurate enough for comparative purposes. Fig. 2 demonstrates the prolonged carriage of streptococci, the reduction over time of the positivity of throat cultures, and the contagiousness of the acutely ill patient in relationship to the occurrence of rheumatic fever.

These studies suggest that the important observation to make when attempting to interpret a positive throat culture is *when the patient acquired the organism initially.* The eventual harm to the patient and to those around him or her is related directly to that time. We use epidemiology, clinical findings, and culture to determine the time of the initial infection. None of these is absolute, but if the epidemiologic findings are compatible, the patient has clinical streptococcal disease, and large numbers of streptococci are grown on throat culture, there is little doubt that a bona fide infection is present. The opposite is true if data do not fit the pattern. My advice is to select very carefully by epidemiologic and clinical methods those patients in whom throat cultures or other methods of identifying the streptococcus will be performed, attempt to relate all findings to the *onset* of streptococcal infection, and manage the patient accordingly.

ERADICATION OF STREPTOCOCCUS FROM PHARYNX

The persistence of streptococci after treatment with antimicrobial agents has varied sharply from study to study, from 5% to 25%.[9] Among the variety of reasons for this wide variation, the one that has been the hardest to control is distinguishing acute infections from the prolonged carrier state. Although the data are not complete, it is probably more difficult to eradicate the chronic carrier state than acute infection. Failure or inability to address this issue clouds the interpretation of results of some studies addressing the problem of eradication.

Antimicrobial resistance. Antimicrobial resistance is

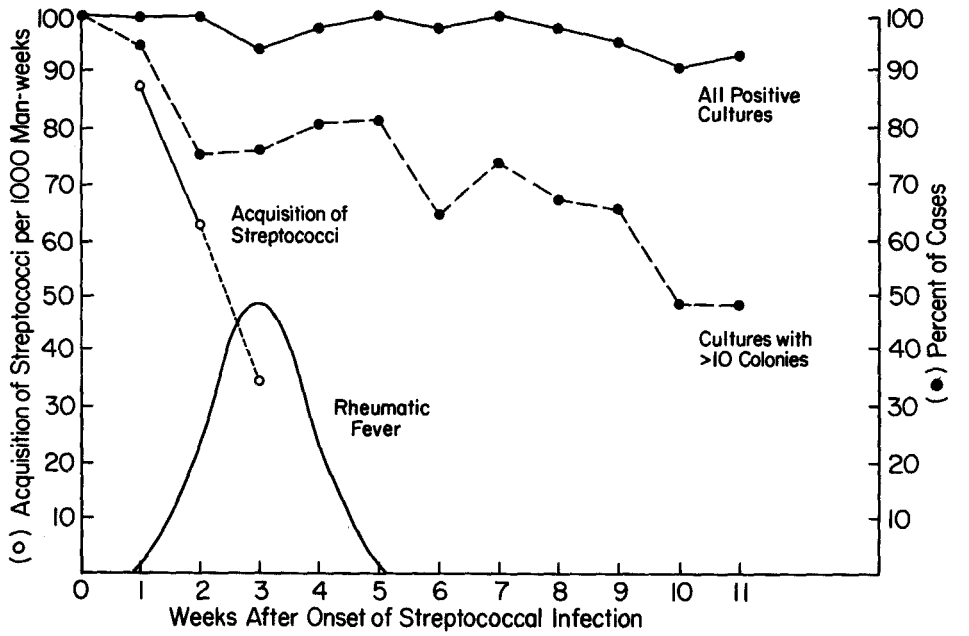

Fig. 2. Role of pharyngeal carrier state in streptococcal infections and rheumatic fever. *Hatched line* showing acquisition of streptococci denotes that point at 3 weeks represents values for 3 weeks plus later times. (From Denny FW. Circulation, in press.)

potentially serious.[10] Fortunately, the group A streptococci have not developed resistance to penicillin or, so far as I have been able to ascertain, to the cephalosporins. There has been widespread resistance to the tetracyclines for many years. Resistance to the sulfonamides was a serious problem during World War II, but has not been a problem when they are used for prophylaxis in civilian populations. The sulfonamides are not effective in eradicating the streptococcus, so should not be used in infected patients; they are, however, effective in prophylaxis.

In the United States, resistance to erythromycin is not yet problematic. There is a rare erythromycin-resistant strain, but as far as I know, there has been no appreciable increase over the past couple of decades. The situation in Japan has been different. In 1971, the percentage of resistant strains was relatively low, about 8%, but has increased rapidly, so that by 1974, 72.3% of strains in one study were resistant, and 62.3% in another study. The resistance to erythromycin has been accompanied by resistance to chloramphenicol and tetracycline. In at least one report, these high levels of resistance have declined somewhat in recent years. We are not now faced with this problem in the United States, but the Japanese experience indicates that pediatricians should be on the alert, because most of us use erythromycin as the drug of choice in children who are allergic to penicillin.

Antimicrobial tolerance. Another mechanism that has been suggested as a possible cause of difficulty in eradicating streptococci by the use of penicillin is the development of tolerance. Allen and Sprunt[11] first called our attention to this in 1978 when they reported 12 strains of group A streptococci with a penicillin G mean inhibitory concentration/mean bactericidal concentration ratio that varied from 8 to 32. More recently this has been reported by Kim and Kaplan,[9] who found that tolerance could be identified in 25% of isolates in a treatment failure group, in contrast to none of the strains in a treatment success group. Similar results have been reported from Israel.[12] In contrast, Fierman et al.[13] and Feldman et al.[14] have reported that tolerance did not seem to play a role in the eradication of streptococci from the pharynx. Furthermore, Kaplan's group[15] reported recently that tolerant strains were no more common in penicillin failures than in successes. They suggest that several factors may influence the penicillin failure rate in group A streptococcal pharyngitis. These published data show that group A streptococci can develop penicillin tolerance, but its role in the failure to eradicate streptococci from the throat remains unclear.

β-Lactamase-producing bacteria. The role of β-lactamase-producing bacteria in the tonsillar pharynx in the failure to eradicate streptococci by use of penicillin is even more controversial. As far back as 1964, it was suggested

that the presence of *Staphylococcus aureus* that produced β-lactamase might be important in eradication failures.[16] Several studies that followed this observation gave differing results, including one by Quie et al.[17] that showed no effect of this phenomenon. Subsequent studies in several laboratories have shown that other bacteria, including bacteroides, haemophilus, and branhamella species, may also play a role in this phenomenon.[18-21] The bulk of evidence suggests that such organisms may play a role in the failure to eradicate streptococci from the throat. This comes primarily from studies that show that antimicrobials that are not affected by β-lactamases may be somewhat more effective in eradicating streptococci than is penicillin.[15, 22] It would seem worthwhile to keep this phenomenon in mind and, should the data become definitive in the future, make appropriate changes in our management of streptococcal sore throats.

A possible solution to some of these problems is presented by recent data that suggest that when antibiotics resistant to β-lactamase are used or added to penicillin regimens, the eradication of streptococci is increased. Chaudhary et al.[23] first reported that the treatment of group A streptococcal pharyngitis with oral penicillin V and rifampin was more effective than with penicillin V alone. Tanz et al.[24] reported subsequently that in studies of carriers, intramuscular benzathine penicillin plus oral rifampin for 4 days was considerably more effective than benzathine penicillin alone. As mentioned, several studies have suggested that antimicrobials other than the penicillins, which are affected by β-lactamases, are more effective in eradicating the streptococcus.[15, 22] It is difficult to know what to do with these data. Although penicillin G is still considered the drug of choice in treating streptococcal pharyngitis, there are always some patients who have persistent positive cultures despite adequate penicillin therapy. I think it might be prudent in some of these patients to add rifampin to a penicillin regimen or to use another antibiotic. Further data should help clarify this puzzling situation.

RAPID DIAGNOSIS OF STREPTOCOCCAL PHARYNGITIS

This new method of diagnosis is exciting and represents a truly new advance in the management of streptococcal pharyngitis.[25-27] Because rapid diagnostic techniques have become so widely available and the publications so numerous, I will summarize only what I think is the present status of their use. The sensitivity, specificity, positive predictive value, and negative predictive value in published studies are quite good.[28] As might have been anticipated, most of the problems with sensitivity are caused by the failure of tests to detect the small numbers of streptococci that may be found on throat culture. This raises the knotty problem of the interpretation of small numbers of streptococci in throat cultures, as already discussed. Gerber et al.[29] may have answered this question in a recent publication; children with small numbers of streptococci on throat cultures but with negative rapid diagnostic test results responded with an elevation in antistreptolysin 0 titer as frequently as did those with large numbers of streptococci. This suggests that the inability of the rapid test to detect small numbers of streptococci may result in the failure to detect and treat some bona fide infections, an undesirable situation. As more studies are reported, the success of the rapid diagnostic test is not quite as dramatic as first thought.[30] There are additional problems with the antigen detection tests: they are expensive, and unless a practice is large enough that laboratory personnel are available to perform the tests, they can be disrupting and sometimes impossible for the practitioner to utilize.[31] It would seem that the appropriate use of the rapid diagnostic tests at present is in suspected streptococcal pharyngitis. If the test results are positive, it can be assumed with some confidence that a throat culture will be positive, and the culture can be omitted. On the other hand, if the results are negative and the diagnosis of streptococcal infection still questionable, a throat culture should be done and treatment given according to the results.

EFFECT OF TREATMENT ON SYMPTOMS AND SIGNS OF STREPTOCOCCAL PHARYNGITIS

I had the most fun with this part of this Memorial Lecture, because the effect of treatment has been of interest to me since my Wyoming days. This interest was rekindled by several articles in the January 1984 issue of *Pediatric Infectious Disease*. In the newsletter, or yellow pages, of that issue, there appeared a section entitled "The Issue is Settled." The editor stated that Nelson's[32] article in that issue presented data that clearly established the efficacy of penicillin in relieving symptoms in children with streptococcal pharyngitis, and the editorial by Hall and Breese,[33] which reported the reanalysis of data from two studies that have been cited for years as demonstrating the ineffectiveness of penicillin in altering the clinical course of streptococcal pharyngitis, showed that penicillin worked. Nelson's report suffered by the small number of patients involved, by the fact that the patients were not examined at frequent intervals, and because the investigator was not blinded to assignment of therapy. This article and the accompanying editorial reanalyzing some of the data from the Wyoming studies[34, 35] interested me. It also caused some concern on my part, not only because the previous studies done by the Wyoming group were being so misin-

terpreted, but because the recent articles appeared to me to give greater emphasis to this matter than I think is warranted. They seemed to encourage antimicrobial treatment without adequate attention to other important aspects of management. In a response, I pointed out that the Wyoming papers had been misinterpreted and why I was concerned with some of the newer data being published.[36] The Wyoming studies showed clearly that antimicrobial agents shortened the course of streptococcal pharyngitis. We did state that the degree of amelioration of symptoms and signs was not great, and we did emphasize that acute streptococcal infections were self-limited diseases without any therapy. We also emphasized that the main reason for treating streptococcal infections at that time was to prevent acute rheumatic fever. I believe this reasoning was and still is correct. I believe also that the clinical situation in the 1980s is different. Rheumatic fever is a less serious problem and the social situation in the United States is vastly different. Many, if not most, mothers work outside of the home, and any shortening of duration of an acute disease may be worth the cost and risk of antimicrobial therapy. I think it is appropriate to assume that treatment of streptococcal infections does shorten the course of disease if used early. The Wyoming studies, and recent well-controlled studies showing similar results in children,[37,38] should not be license to treat all sore throats with penicillin with the hope that the clinical course will be shortened. Patients should be managed with thorough attention to the epidemiologic, clinical, and laboratory aspects of disease, and only those patients who the physician believes can benefit materially by treatment should receive an antibiotic.

OTHER BACTERIA AS CAUSES OF PHARYNGITIS

Assessment of the various causes of pharyngitis indicates that nonbacterial agents, almost certainly viruses, are the cause of the majority of cases. It seems certain, too, that the group A streptococcus remains the most important bacterial cause of pharyngitis. While rheumatic fever was common, this etiologic approach to pharyngitis presented no significant problems, because it seemed clear that we should concentrate on streptococcal pharyngitis. Now that rheumatic fever may be less frequent and it is understood that treatment may shorten the clinical course of streptococcal disease, we should probably be more concerned that other bacteria may cause pharyngitis and that these infected patients also may benefit from treatment. Interest in this problem was highlighted in an article by Komaroff et al.,[39] who reported a study of pharyngitis in 763 adults. In serologic studies, they found that *Chlamydia trachomatis* and *Mycoplasma pneumoniae* were more common than

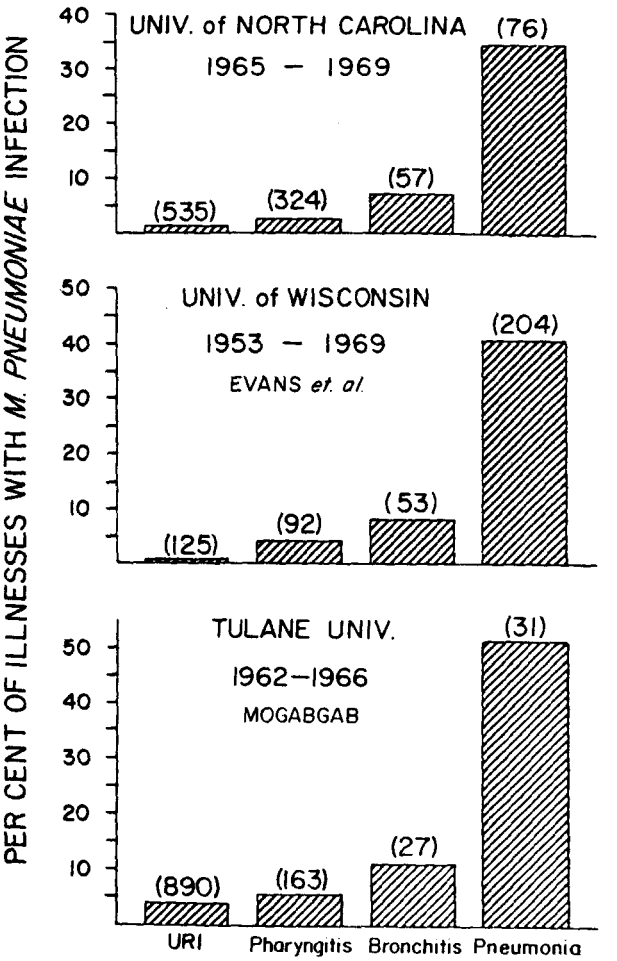

Fig. 3. Association of *Mycoplasma pneumoniae* infection with acute respiratory illness in university students. Number of illnesses studied, in parentheses. (From Denny FW, Clyde WA Jr, Glezen WP. J Infect Dis 1971;123:74-92.)

group A streptococci in causing pharyngitis in adults. These data prompted examination of the status of both of these organisms as causes of pharyngitis, as determined by others before and after the paper published in 1983.

Chlamydia trachomatis. Three studies have been published recently on the etiologic role of *C. trachomatis* as a cause of acute pharyngitis in college students, in patients from a family medicine clinic and an employee health service in a hospital, and in school-aged children.[40-42] None of these studies detected *C. trachomatis* in any patients. These data are in contrast to those of the Boston group, and suggest that we should be cautious in incriminating *C. trachomatis* as a significant cause of pharyngitis at this time. There seems little doubt, however, that chlamydia can infect the upper respiratory tract as well as the genital tract, as indicated by the simultaneous occurrence of

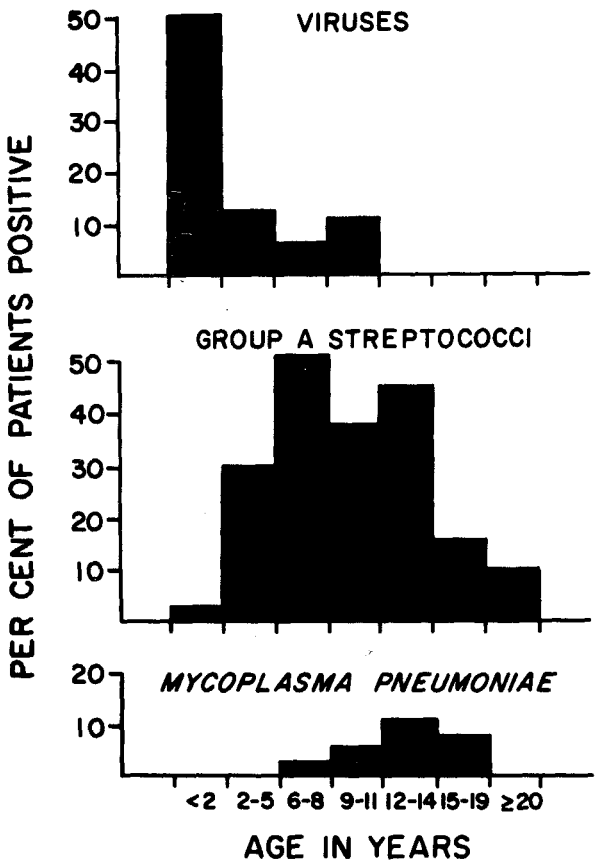

Fig. 4. Frequency of recovery of microbial agents from patients with pharyngitis, by age, Chapel Hill, North Carolina, 1964-1965. (From Glezen WP, Clyde WA Jr, Senior RJ, Sheaffer CI, Denny FW. JAMA 1967;202:119-24. Copyright 1967, American Medical Association.)

pharyngitis and urethritis in a young adult man.[43] A report of pharyngitis caused by *Chlamydia psittaci*, strain TWAR, in one of 150 college students is also of interest.[44]

Mycoplasma pneumoniae. The status of *M. pneumoniae* may be different from that of *C. trachomatis*. Studies in university students in the late 1950s and 1960s in North Carolina,[45] Wisconsin,[46] and Louisiana[47] showed that although pneumonia was the principal disease produced by *M. pneumoniae*, other syndromes in the respiratory tract, including pharyngitis, were associated with mycoplasma infections (Fig. 3). Subsequent studies in children seen in a pediatric practice in Chapel Hill, North Carolina, during the 1960s enlarged on these findings.[48] Children younger than 5 years of age rarely have clinical disease. On the other hand, children older than 5 years were shown to be infected frequently, including infections diagnosed as pharyngitis. The age distribution of patients who have pharyngitis caused by viruses, group A streptococci, and *M. pneumoniae* differs, with *M. pneumoniae* occurring in older children (Fig. 4).[45] The symptoms and physical findings in patients with *M. pneumoniae* disease were similar to those infected with the group A streptococci or with viruses. These data suggest that these illnesses cannot easily be distinguished by history or clinical examination and that *M. pneumoniae* is a significant but not frequent cause of pharyngitis. The relative paucity of *M. pneumoniae* infections in the past few years has hampered attempts to clarify the role of this organism as a cause of pharyngitis.

Non-group A streptococci. In addition to the possible etiologic role of non-group A streptococci in pharyngitis, these organisms are important for several reasons. Non-group A streptococcal colonies, especially groups C and G, are easily confused with group A colonies on blood agar plates unless definitive techniques for separating them are used. In addition, nephritis can follow group C streptococcal infections.[49]

There seems to be little question that groups C and G can produce epidemic infections, usually but not always food-borne.[50-53] Groups C and G make streptolysin O similar to that of group A, and the antistreptolysin O test has been used to confirm host responses in the reported studies. It seems clear that groups C and G are causes of epidemic infections; the problem is in establishing the relative role of these organisms as causes of endemic disease.

This problem has been of interest for many years. A study performed by the Commission on Acute Respiratory Diseases at Fort Bragg during World War II, and published in 1947,[54] interests me because although Lewis Wannamaker and I were not involved with the Commission before 1948, this group subsequently moved to Cleveland and formed the nucleus of the department in which we started. They showed that some patients from whom group C and G were isolated developed antistreptolysin O or antifibrinolysin responses; of the patients who had an immune response, 86% had group A infections, 7% had either group C or group G infections. These data indicated that the group A streptococcus in these young military personnel was of prime importance, and relegated groups C and G to a minor role.

There is more evidence linking other groups of streptococci to clinical disease. Routine throat culture surveys in both children and adults reveal that these organisms are isolated frequently[55-58]; results of studies in children and adults with pharyngitis support these observations.[56, 57, 59-61] All studies show that groups C and G predominate; group B organisms are also found frequently, but group F streptococci appear so infrequently that they probably do not warrant further mention. Recent studies from Malay-

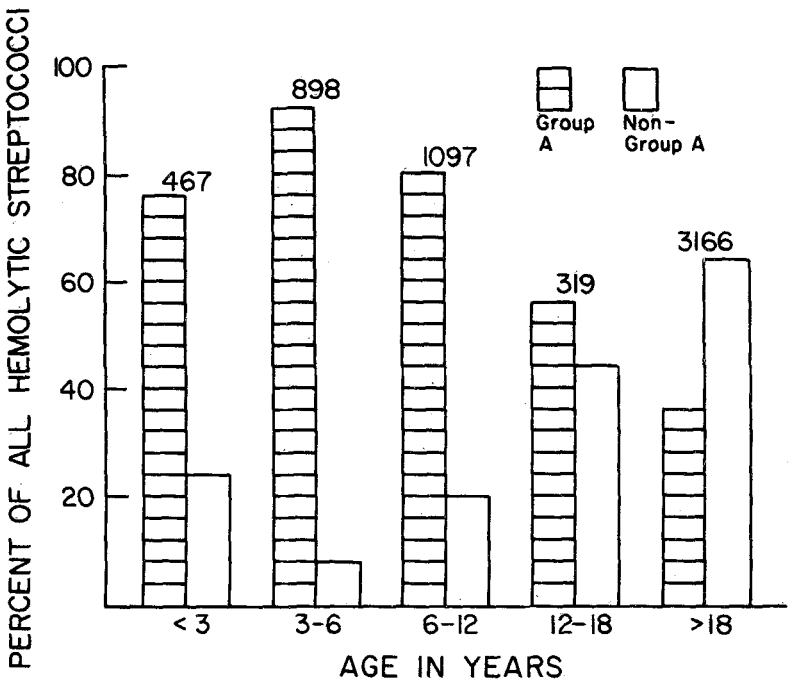

Fig. 5. Group A and non–group A hemolytic streptococcal isolates by age, North Carolina Memorial Hospital, 1977-1984. (Courtesy H. J. Hamrick, MD.)

sia, Israel, Japan, England, and Nigeria all confirm that non–group A organisms, primarily C and G but occasionally B, are found in carriers and in infected children and adults.[62] A study from Nigeria suggests that these organisms may be associated with skin as well as throat infections.[63]

Hamrick a member of our group at the University of North Carolina, recently gathered data (unpublished) on the breakdown between group A and non–group A streptococcal isolates from patients with clinical pharyngitis over several years, as determined by our routine bacteriology laboratory (Fig. 5). Non–group A streptococci were isolated slightly more frequently in the very young child than in the child of school age; after that, the percentage of non–group A organisms increased rather dramatically, so that in individuals older than 18 years of age, approximately 60% of organisms isolated were not group A. These data support the earlier studies, and suggest that careful attention should be given to the age of patients studied in order to elucidate the problem of non–group A streptococci as causes of pharyngitis.

Other bacteria. For completeness, several other organisms should be mentioned. There are scattered reports of *Neisseria meningitidis* and *Neisseria gonorrheae* associated with acute pharyngitis. I have been able to find one report that *Haemophilus influenzae* may be as well.[64] I do not doubt that the gonococcus can be associated with pharyngitis. I am particularly interested in the possibility that *H. influenzae* is also associated with acute upper respiratory tract infections, not just otitis media and sinusitis. I have a hunch that this may be correct.

OTHER PROBLEMS AND OBSERVATIONS

Several other important problems in the management of pharyngitis are mentioned only for completeness. The frequency of administration and the dosage of all antibiotics remain important questions. Maybe most important is the question of the cost effectiveness or cost benefit of the treatment of streptococcal pharyngitis in this era when rheumatic fever appears to be disappearing. I have great difficulty in interpreting the literature on this subject. It is unfortunate that the proponents of this approach are unable to put any value on streptococcal infections except that of the dollar. This is so disconcerting to me that I cannot come to grips with the problem, either for you or for me. Somehow, I believe that Lewis Wannamaker would agree with my reluctance.

I have saved until the very last what may be the most interesting and exciting of all of the recent observations: the reappearance of rheumatic fever in the United States. This was heralded by the Utah experience with 76 cases from 1985 to 1986, of which 56 patients had carditis.[65]

Reports from Hawaii, Akron and Columbus in Ohio, western Pennsylvania, Denver, and Dallas suggest that this phenomenon may be widespread.[66-71] I have had experience with more patients during this past year than for quite a number of years. It is entirely possible that the wane in incidence of rheumatic fever was simply a natural phenomenon and that we are heading into another era when it will be a very important disease in the United States. If rheumatic fever returns, it will once again change our management strategy.

I have attempted to evaluate the status of a selected group of problems in the management of pharyngitis in 1986, with emphasis on the streptococci. This group of organisms continues to challenge us. The progress made in recent years has been good, and the future bodes well for even greater advances.

Let me say again what a privilege and a pleasure it has been to give this lecture in memory of Lewis Wannamaker. We owe so much to him for his great contributions in this field, and I am sure he would be proud to see that so many of the things that he began continue to bear fruit.

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