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*THE PRESBYTERIAN AND BABIES HOSPITALS, NEW YORK, N.
Y., IN THE YEARS 1936-1942***

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THE ASSOCIATION OF TYPE SPECIFIC HEMOLYTIC STREPTOCOCCI WITH ACUTE GLOMERULONEPHRITIS¹

AT THE PRESBYTERIAN AND BABIES HOSPITALS, NEW YORK, N. Y., IN THE YEARS 1936-1942

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INTRODUCTION

The mechanism by which acute glomerulonephritis develops is unknown, but there is general agreement that an infection initiates the process. This infection commonly occurs in the upper respiratory tract but classical instances of acute glomerulonephritis have followed infections of the skin, subcutaneous tissues, lungs and peritoneal cavity. An antecedent hemolytic streptococcal pharyngitis has not been excluded in all these instances. Clinical, bacteriological and immunological evidence indicates that the hemolytic streptococcus is the precipitating agent in the great majority of the infections that precede acute glomerulonephritis (1-7). It should be noted, however, that acute glomerulonephritis has followed pneumococcal pneumonia (8), subacute bacterial endocarditis (9), and gastrointestinal infections due to various enteric organisms (1).

Recently Rammelkamp, Weaver, and Dingle (10) presented evidence indicating that the attack rate of acute glomerulonephritis following Group A hemolytic streptococcus infections varied considerably. In contrast, the incidence of acute rheumatic fever following such infections appeared to be relatively constant. Rammelkamp and his associates postulated that this difference in attack rate was due to the episodic appearance of certain strains of hemolytic streptococci which were more nephritogenic than others. Their collected data

indicated that Type 12 organisms caused most of the infections associated with acute glomerulonephritis. Kempe, Olmstead, and Curnen (11) reported an outbreak of nephritis in a school of 96 young boys. There were four cases of clinical acute nephritis while transitory hematuria was reported in 22 other students. The only typed strain obtained from the students at the school was Group A, Type 12. However, it was not obtained from the patients with clinical nephritis. Manser and Wilson (12) have reported an epidemic of hemolytic streptococcal pharyngitis, presumably milk-borne, associated with a high incidence of nephritis. Throat swabs of 140 people, including patients and contacts, were cultured. Thirty-five Group A streptococci were typed. Sixteen were Type 12, 10 were Type 22, and the remaining were distributed among other types. In contradistinction to these data, Gunn and Griffith (13) in 1928 stated that while Group A, Type 1 hemolytic streptococcus produced the most severe disease with the highest incidence of complications, Type 2 was more likely to cause nephritis and endocarditis. Rammelkamp and Weaver (14) have presented a comprehensive review of this matter.

Stimulated by Rammelkamp, Weaver, and Dingle's work (10) on the association of Type 12 hemolytic streptococci and acute glomerulonephritis observed during the past four years, similar data, which had been accumulated at the Presbyterian and Babies Hospitals in New York City during the years 1936 to 1943, have been re-examined.

METHODS AND DATA

A study was made of all the records of patients at the Presbyterian and Babies Hospitals of the Columbia

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**SEROLOGICAL CLASSIFICATION OF GROUP A HEMOLYTIC STREPTOCOCCI
ISOLATED FROM 90 CASES OF ACUTE GLOMERULONEPHRITIS
OBSERVED AT THE BABIES AND PRESBYTERIAN HOSPITALS
NEW YORK CITY 1936 - 1942**

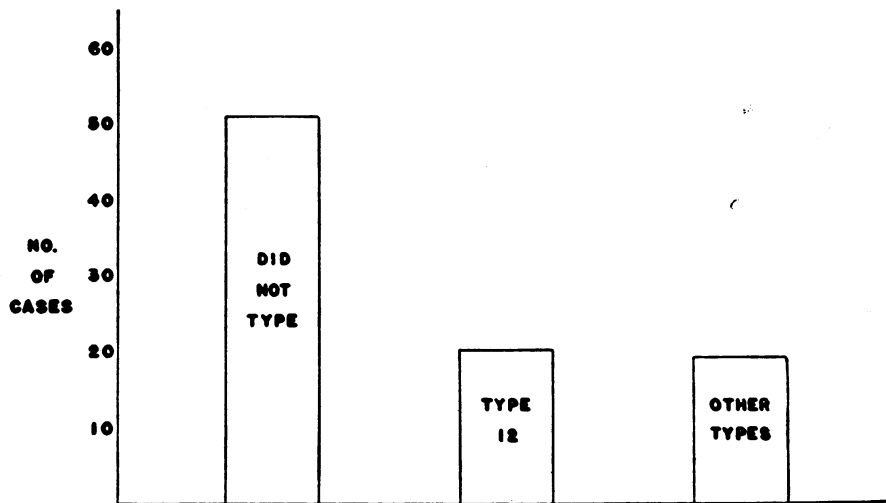


FIG. 1

Presbyterian Medical Center in New York diagnosed as having acute glomerulonephritis. There were 212 individual instances of well documented acute nephritis during the years 1936 to 1943. In 90 of these 212 patients, Group A hemolytic streptococci were cultured from the pharynx (Figure 1). At a later date an attempt was made to type these 90 strains. Thirty-nine exhibited type specificity. Of these, 20 (51 per cent) were Type 12. The remaining 19 were classified into the following Types: 1, 2, 4, 5, 6, 9, 11, 19, 28, 30, 42, or 46.

These data were collected as part of a study on the natural history of glomerulonephritis in childhood and adult life. Nose and throat swabs for the possible isolation of hemolytic streptococci had been taken from a hospital and clinic population composed of patients in various stages of acute, chronic and healed glomerulonephritis. During the period from 1936 to 1943 406 cultures, mainly pharyngeal, yielded Group A hemolytic streptococci. These organisms were maintained in the laboratory by frequent transplants. During the course of the years an attempt was made to determine the type specificity of each of the strains. At the time of the study specific typing sera for hemolytic streptococci were just becoming available so that all organisms were not tested against all present-day sera. The following typing sera⁴ were available at some time during the course of the seven years' work: 1, 2, 3, 4, 5, 6, 8, 9, 11, 12, 13, 14, 15, 17, 18, 19, 22, 23, 24, 26, 28, 29, 30, 31, 32, 33, 36, 37, 38, 39, 40, 41, 42, 43, 44, and 46. Either the slide agglutination method of Griffith (15), the precipitin method of Lancefield (16),

⁴ Generously supplied by Dr. Rebecca C. Lancefield.

or both were used. Only 157 (38.6 per cent) of the 406 strains of Group A hemolytic streptococci could be typed. The failure to type so large a proportion of these cultures may have been due to a loss of the type-specific antigens through long cultivation on artificial media. In some instances these strains may represent types for which no sera were available. Type 12 was obtained most frequently, 24 times, in this group of patients in various phases of nephritis. Nineteen of these were isolated in the four year period between 1939 and 1942. Twenty of the 24 cultures of Type 12 hemolytic streptococci were isolated from patients with acute glomerulonephritis. They were discussed previously. Type 18 was the second commonest streptococcus identified. It was isolated from 10 patients, none of whom had acute glomerulonephritis.

The 39 cases of acute nephritis in which data on type-specific hemolytic streptococci were available, were examined to determine the time relationship between the date of isolation of the hemolytic streptococcus and the stage of the acute nephritis (Figure 2). The day of onset of the nephritis is taken as the initial appearance of edema, proteinuria, hematuria, or encephalopathy or any combination of these classical signs. Healing of the nephritis was dated from the time when the urine became consistently normal.

It will be seen from Figure 2 that the organisms were isolated from four days to six months after the presumed onset of the nephritis. Since the onset of the renal disease occurred two to three weeks after the initiating infection, the patients were not available for cultures until long after their pharyngitis. The significance of pharyn-

ACUTE GLOMERULONEPHRITIS
COURSE OF DISEASE AND TIME OF ISOLATION
OF TYPE SPECIFIC HEMOLYTIC STREPTOCOCCI

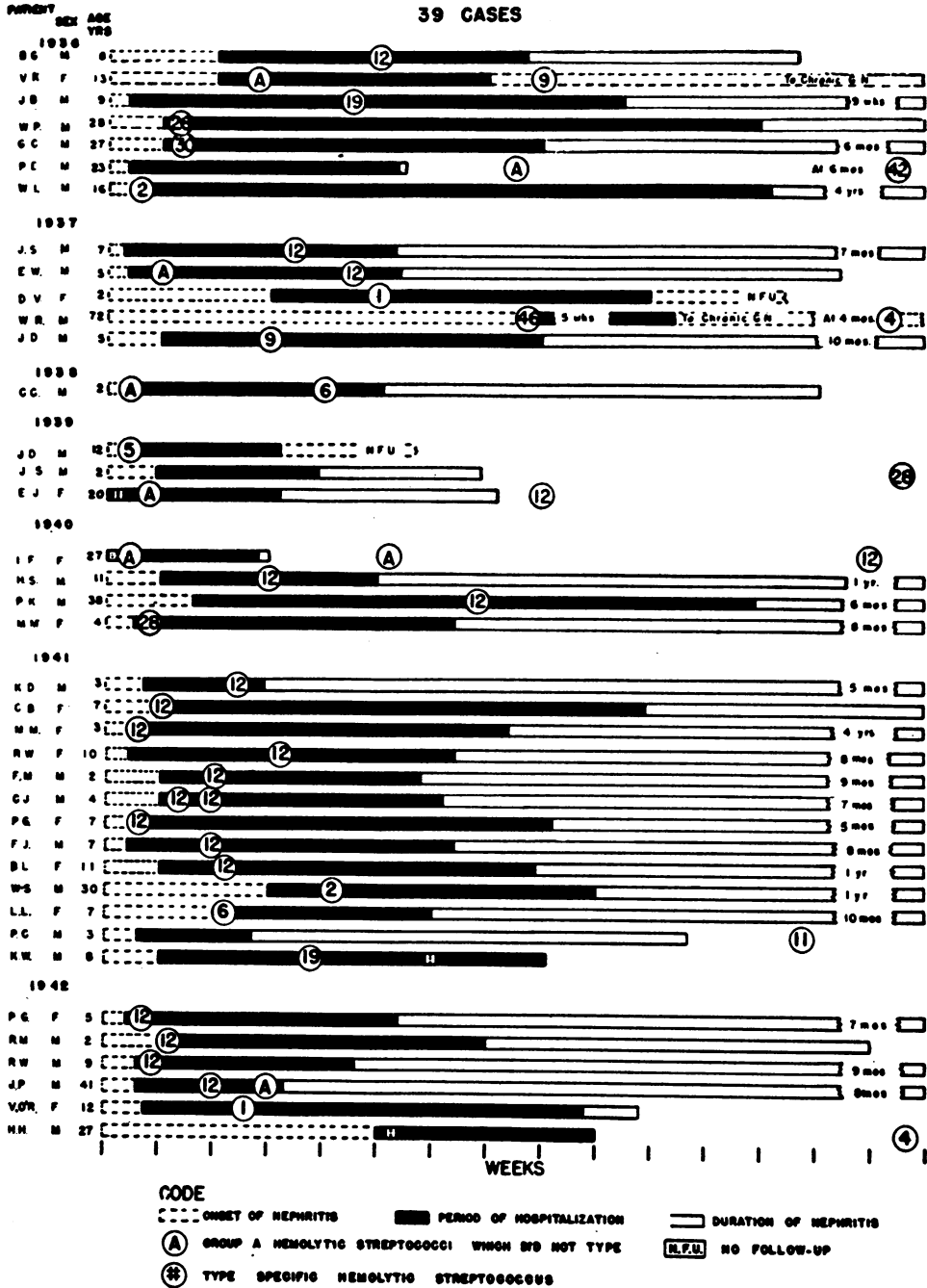


FIG. 2

geal cultures obtained at this time is difficult to evaluate. In studies of the relationship between the types of hemolytic streptococci in early scarlet fever and organisms isolated during later complications (17), it was determined that cultures obtained within the first two weeks showed new types of hemolytic streptococci in at most 20 per cent of instances. After two weeks the likelihood for pharyngeal contamination with new types was increased many times. However, Rammelkamp (18) has stated that in his hands there is at most a 6 per cent contamination of the pharynx with new types in the first two weeks of nephritis. The data in Figure 2 show that 19 of the cultures were obtained within two weeks of the onset of the nephritis. Ten or one-half of the total were Type 12, a figure which is similar to that for the entire series.

A comparison of the nephritic patients in whom Type 12 hemolytic streptococci were isolated with those from whom other types were obtained, reveals no significant difference in either final outcome, presence of suppurative complications, or antistreptolysin "O" response. However, the possibility exists that a preexisting Type 12 organism may have been present in the so-called non-Type 12 group.

COMMENT

Seegal and Earle (19) called attention to certain biological differences between glomerulonephritis and rheumatic fever. They noted that: 1) glomerulonephritis had a uniform geographical distribution throughout North America while rheumatic fever was more frequent in the northern than in the southern latitudes; 2) glomerulonephritis was more common in males than in females, whereas rheumatic fever was equally distributed between the sexes; 3) in two-thirds of the cases of acute glomerulonephritis there was a "deep" hemolytic streptococcus infection, whereas rheumatic fever was usually preceded by a superficial pharyngitis; 4) relapse was a rarity following the healing of acute glomerulonephritis. In contrast recurrence of rheumatic fever was to be anticipated; 5) in acute exacerbation of chronic nephritis there was a shortened latent period between infection and relapse of the disease. In rheumatic fever the latent period remained constant in each exacerbation. Subsequently, Earle, Seegal, Lyttle, Loeb, and Jost (20) showed that in contrast to rheumatic fever the exacerbation in seven of eight cases of nephritis was fully developed before the antistreptolysin titer increased. Recently Fischel and Gajdusek (21) observed a serological difference between nephritis and rheumatic fever. They have shown that complement is sharply reduced in the former but is normal or elevated in rheu-

matic fever. Rammelkamp, Weaver, and Dingle have emphasized another biological difference between the two diseases, namely variation in the attack rate following Group A hemolytic streptococcus infections. The attack rate for glomerulonephritis varies in different outbreaks of hemolytic streptococcal infections, whereas there is a relatively constant incidence (3 per cent) of rheumatic fever after invasion by the hemolytic streptococcus. These workers have presented data which suggest that the variation in incidence of acute glomerulonephritis may be due to outbreaks of infection due to certain nephritogenic strains of hemolytic streptococci. Type 12 seems to be the prime offender. Our data confirm the observation of Rammelkamp, Weaver, and Dingle (10) that some strains of the Group A, Type 12 hemolytic streptococcus may be considered nephritogenic.

Data already at hand indicate that the Type 12 hemolytic streptococcus is quite variable in its ability to initiate acute glomerulonephritis. Rammelkamp, Weaver, and Dingle (10) report a single case of nephritis in 42 patients with Type 12 pharyngitis among a group of air force personnel. In 1939 Coburn and Pauli (22) studied an epidemic of Type 12 infections at the Babies Hospital, New York. These infections preceded by one year the period of high incidence of acute glomerulonephritis and Type 12 hemolytic streptococcus infection reported in our series. Coburn (23) stated that nephritis was not known to have developed in any of these 38 patients studied by him.

There are certain limitations to the data presented here. First, cultures were obtained at various intervals after the onset of the nephritis and not at the time of the initiating infection. Therefore, the possibility exists that new types of hemolytic streptococci might have been introduced. Second, only one or two colonies were selected for subculture from the original streaked plate. If more than one type of hemolytic streptococcus were present in the pharynx they might have been missed. However, Schwentker, Janney, and Gordon (24) concluded from their studies "that the need for picking multiple colonies from throat culture plates is greatest for healthy carriers, less for convalescent carriers and practically negligible for patients with acute streptococcal throat infections." Third, type specificity was probably

often lost during the course of repeated subculture on artificial media. Finally, type-specific organisms may have been present for which corresponding anti-sera were not available.

SUMMARY AND CONCLUSIONS

1. During a seven year period, 1936 to 1942, at the Presbyterian and Babies Hospitals in New York City type-specific strains of Group A hemolytic streptococci were isolated from 39 patients with acute glomerulonephritis.

2. Twenty (51 per cent) of these 39 cultures were identified as Type 12.

3. A variety of different types of Group A hemolytic streptococci were isolated from the remaining 19 patients.

4. The data presented are in accord with the observations of Rammelkamp, Weaver, and Dingle that Type 12 hemolytic streptococcal infections are frequently followed by attacks of acute glomerulonephritis.

5. Certain of the biological differences between acute glomerulonephritis and rheumatic fever are discussed.

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