SEROLOGICAL EXAMINATION OF HAEMOLYTIC STREPTOCOCCI FROM ACUTE RHEUMATIC AND CONTROL GROUPS

BY

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The association between inflammation of the upper respiratory tract and the rheumatic state has long held clinical recognition. The evidence on which this has been based was supported by the frequency with which tonsillitis occurred in rheumatic patients, statistical data being supplied by the work of St. Lawrence (1920), Ingberman and Wilson (1924), Poynton (1925), Bertram (1925), and McCulloch and Irvine-Jones (1929). In these investigations the incidence of throat infections was found to vary from 22.4 per cent. to 77 per cent. Additional proof of the prevalence of repeated infection was found in the condition of the fauces. Thus the St. Thomas's Hospital data in the Medical Research Council (1927) Report on rheumatism showed that the proportion of healthy throats in children of non-rheumatic families was greater than that in rheumatic families. In a similar controlled investigation Lambert (1920) found that in 1,000 consecutive cases of rheumatism the proportion of unhealthy tonsils was 25.3 per cent., as compared with 17 per cent. in 250 cases of acute pneumonia. Active infection as indicated by inflammation of the throat was present in 22.4 per cent. and 0 per cent. of rheumatic and control groups respectively. Perhaps a more striking demonstration of the connexion between the two conditions is supplied by the occurrence of outbreaks of rheumatism, mainly of recurrent attacks but sometimes primary, after epidemic tonsillitis. Many examples of this sequence are described in the literature by Raven (1923), Boas and Schwartz (1926), Hiller and Graef (1927-8), Glover (1930), Schlesinger (1930), Glover and Griffith (1931), Collis (1931), Sheldon (1931), Bradley (1932), and Coburn and Pauli (1935).

While there is thus considerable evidence for the occurrence of tonsillitis in rheumatism, the bacteriological examination of the throat flora in such cases has yielded divergent results. Although the streptococcal genus has attracted most attention, many species within the genus have been incriminated by different observers. Thus the work of Poynton and Paine (1900) stressed the importance of the alpha haemolytic or *viridans* streptococci. On the other hand, Small (1927) and Birkhaug (1927) separately claimed aetiological significance for gamma or indifferent streptococci. Within recent years, however, beta haemolytic strains have gained increasing recognition in the reports of Glover (1930), Coburn (1931), Glover and Griffith (1931), Collis (1931), and Bradley (1932). Similar investigations, such as that described by Schlesinger (1930), have led to the view that no single type of organism could be recognized as responsible for all infections, but that many species were involved. It may be noted that in the majority of investigations in which beta haemolytic streptococci have appeared important the type of nasopharyngeal infection has been of the epidemic variety in enclosed populations such as those of schools, hospitals, and training quarters. Thus the importance of Mantle's observation in 1885, at the beginning of the bacteriological era, that rheumatism was a more common complication of infectious sore throat than of sore throat of a non-infectious nature, becomes manifest. Even in sporadic

cases of rheumatism, such as in the series of Gibson, Thomson, and Stewart (1933), beta haemolytic streptococci were isolated from the throat secretions of 43 per cent. of patients, as compared with 20 per cent. of controls. It is commonly recognized that haemolytic streptococci from human sources differ greatly in pathogenicity as determined by virulence tests in experimental animals; but the method is not suitable for extensive investigations, nor does the pathogenicity in man and animal always concur. Lancefield (1933), by means of a precipitin reaction, claimed that haemolytic streptococci could be divided into groups, each of which possessed a common, group-specific carbohydrate fraction (M). Furthermore, Group A represented the important pathogens in the human subject. An important practical application of this test was the demonstration by Lancefield and Hare (1935) that the majority of strains causing puerperal infection of the uterus were Group A in character, whereas the majority of strains in the birth canal during a normal puerperium were not. As Lancefield (1935) suggested, the main source and habitat of Group A strains is probably the human nasopharynx, but not all commensal strains in this site belong to Group A. Hare (1935) for instance, examining the nose and throat of normal human beings, noted that only about one-third of haemolytic streptococci isolated were Group A, the carrier rate of this type in a normal population being estimated to be approximately 7 per cent. The relatively low proportion of commensal Group A strains in normal persons has been confirmed by Davis and Guzdar (1936), who recorded a carrier rate of 3 per cent. Again, Plummer (1935) classified all but two of 418 strains from human infections in Group A, but found that many strains from healthy subjects were not of this group. However, a much higher proportion of carriers has been recorded by Kodama (1937), who found that 68 per cent. of fifty normal subjects were in this category.

Clearly this method of examination may yield information concerning the part played by haemolytic streptococcal infection of the nasopharynx in rheumatic subjects, and the present paper records data obtained by its application.

Methods

ISOLATION OF STRAINS

On admission to hospital with rheumatic manifestations a throat swab from every patient was plated on 5 per cent. horse-blood agar. Incubation was maintained at 37° C. for twenty-four hours under aerobic conditions. If colonies of haemolytic streptococci appeared, several were replated, and from the second plate, if a pure growth resulted, stock cultures were prepared by inoculation of a tube of cooked meat medium. After twenty-four hours' incubation at 37° C. the stock culture was stored at 0° C. Throat swabs from control subjects were similarly treated.

PRECIPITIN REACTIONS

Rabbit antisera against representative strains of Lancefield groups A to H were prepared by serial inoculation of formalinized cultures over a period of six to ten weeks. The carbohydrate antigen required for the test was prepared by inoculating a 5 c.cm. horse-digest medium from the stock culture of the strain under investigation. After twelve hours' incubation at 37° C. the 5 c.cm. broth culture was added to 50 c.cm. of the same medium. The heavy growth after eighteen hours' incubation was deposited by centrifugation and washed four times in sterile normal saline. After the final washing 2 c.cm. of sterile saline, containing hydrochloric acid to a concentra-

tion of N/20, was added to the deposited cells, and the mixture transferred to a water bath at 100° C. for ten minutes. After rapid cooling and centrifugation the supernatant extract was removed and neutralized by the addition of sodium hydroxide. The clear supernatant fluid after further centrifugation was the antigen used in the test.

Results

For this investigation two groups of subjects were selected, each numbering 200 and constituted as follows:

Group R.—Patients admitted to hospital with one or more symptoms of acute rheumatism, including arthritis, carditis, chorea, etc. This group included subjects with both initial and recurring attacks.

Group NR.—Patients in the same hospital wards as members of Group R, but without existing or previous manifestations of rheumatism. This group included all types of diseases, and no discrimination was made as to the presence or absence of nasopharyngeal infection, as will be seen hereafter.

HISTORY OF THROAT INFECTIONS

At the time when a throat swab was taken every patient was questioned as to the occurrence of any symptoms of nasopharyngeal infection during the preceding six weeks. As indicated in Table I, in 156, or 78 per cent.,

TABLE I.—*Results of Throat Swab Examination in Rheumatic Group (R) and in Control Group (NR)*

	Rheumatic Group (R)	Non-Rheumatic Group (NR)
History of recent nasopharyngeal infection	156 (78%)	93 (46%)
Haemolytic streptococci isolated ..	95	26
No history of recent nasopharyngeal infection ..	44 (22%)	107 (54%)
Haemolytic streptococci isolated ..	21	33
Total number from whom haemolytic streptococci were isolated..	116 (58%)	59 (30%)

of the rheumatic group R a history of such an infection was obtained. On admission to hospital with rheumatic manifestations the throat symptoms had entirely subsided in the majority of cases, although enlarged tonsils were often found. Turning to the control group NR, a high figure of recent infection was also found—namely, in 93, or 46 per cent.

INCIDENCE OF HAEMOLYTIC STREPTOCOCCI IN THROAT SECRETIONS

From the throat swabs taken on admission from Group R, haemolytic streptococci were isolated in 116, or 58 per cent. of patients. In the case of the control group NR, fifty-nine, or 30 per cent., were found to be carriers. Considering the results in respect of recent throat infection, ninety-five, or 60 per cent., of the 156 rheumatic patients with a positive history gave positive cultures of haemolytic streptococci, whereas twenty-one, or 47 per cent., of the remaining forty-four with a negative history yielded positive cultures. In the control group NR the haemolytic streptococcal carrier rates in these patients with and without known recent infection were 28 and 30 per cent. respectively.

SEROLOGICAL TYPES OF STRAINS

Applying the precipitin test in the examination of all strains of haemolytic streptococci isolated from the two groups of patients the results detailed in Table II were

TABLE II.—*Serological Grouping of Haemolytic Streptococci Isolated from Throat Swabs of Both Groups*

Lancefield Group	Rheumatic Group (R)				Non-Rheumatic Group (NR)			
	No. of Strains from Patients with Recent Nasopharyngeal Infection	No. of Strains from Patients with no Recent Nasopharyngeal Infection	Total	Percentage of Total No. of Strains (116)	No. of Strains from Patients with Recent Nasopharyngeal Infection	No. of Strains from Patients with no Recent Nasopharyngeal Infection	Total	Percentage of Total No. of Strains (59)
A	84	17	101	87	18	7	25	42
B	2	1	3	3	2	7	9	15
C	4	2	6	5	3	13	16	27
D	0	0	0	0	0	1	1	2
E	0	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0	0
G	5	1	6	5	2	4	6	11
H	0	0	0	0	1	1	2	3
Total	95	21	116	100	26	33	59	100

obtained. The most important of the data secured was the high proportion of Group A strains isolated from Group R patients as compared with Group NR. Whereas the difference in incidence of haemolytic streptococci—namely, 58 per cent. and 30 per cent. respectively—in these two groups was notable, the difference in the incidence of Group A infection was even more significant, the respective incidences being 50.5 and 12.5 per cent. Further, it was found that although the majority of persons in the control group with a history of recent infection were Group A carriers, only seven of thirty-three persons without recent symptoms were carriers. On the other hand, rheumatic subjects irrespective of subjective symptoms of infection yielded Group A strains in the majority of instances where haemolytic streptococci were isolated.

Commentary

The number of subjects in each of the two groups examined was considered large enough to enable reasonable comparison to be made. A high incidence of sore throats in the rheumatic group—namely, 78 per cent.—was not unique, but approximated to that found by St. Lawrence (1920) and Ingeman and Wilson (1924). In an unselected control group it was surprising to find the incidence of recent sore throats to be as high as 46 per cent., but for purposes of comparison in regard to the bacteriological investigations this was a fortunate circumstance. As haemolytic streptococci were recovered from 58 per cent. of all rheumatic subjects on admission to hospital an indication was obtained of the extent to which this type of organism was responsible for the preceding throat infection noted in many of the series examined. It is recognized that faucial infections with this organism, as in scarlet fever, are followed by the carrier condition for indefinite periods, and it was reasonable to assume the same sequence in the present investigation. Of rheumatic patients with subjective symptoms of preceding infection 60 per cent. yielded haemolytic streptococci, whereas in the symptomless the carrier rate of 44 per cent. was still high. On the other hand, in the control group, despite the prevalence of apparent recent infection, only 30 per cent. yielded haemolytic streptococci, and approximately the same proportion of carriers was found in those with and without a recent history. This would suggest either

that in the control group many of the throat infections were due to organisms other than haemolytic streptococci, or that the carrier condition after faucial infection was less persistent than in rheumatic subjects.

Regarding the Lancefield grouping of the isolated strains, it was interesting to find that 87 per cent. of those from rheumatic subjects were of the important pathogenic Group A, whereas only 42 per cent. of strains from controls were of this type. Nevertheless even in the control group the majority of carrier strains from persons with a definite history of recent infection were also members of Group A.

Conclusions

1. Of a group of 200 subjects with acute rheumatic manifestations 78 per cent. gave a history of antecedent throat infections; 46 per cent. of a non-rheumatic control group gave a similar history.

2. Throat swab cultures for haemolytic streptococci were positive in 58 per cent. and 30 per cent. of the rheumatic and control groups respectively.

3. Of the strains of haemolytic streptococci from throat swabs of rheumatic subjects 87 per cent. were serologically classified in Lancefield Group A; 42 per cent. of strains from non-rheumatic controls were of this group. Group A strains were therefore isolated from 50.5 per cent. and 12.5 per cent. of the rheumatic and control groups.

4. The evidence supports the relationship between infection with haemolytic streptococci and the rheumatic state.

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ACUTE EPIDURAL ABSCESS

BY

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Recorded cases of acute epidural abscess are still uncommon, and even more rare are reports of recovery. Hence I feel justified in describing one further successful case.

Dandy in 1926 collected twenty-five cases from the literature; of these, four were diagnosed during life, two ending in recovery, the mortality therefore being 50 per cent. Abrahamson, McConnell, and Wilson in 1934 were able to collect records of sixty cases. Operation had been performed in thirty of these, with survival in twenty—a total mortality of 66 per cent. In many of those operated on the recovery was incomplete. Craig and Doyle, who in 1932 reported a case in which operation was successful, came to the conclusion that up to that time Pulvirenti's was the only authentic case of complete recovery. Incorrect as this statement appears to be in view of MacDonald's case report in 1928, it shows how extremely small must be the number of cases where full recovery has followed operation. It will thus be seen that the prognosis in the untreated case is uniformly fatal. There is no recorded instance of recovery without the aid of surgical intervention.

Pathology

The epidural space exists only on the dorsal aspect of the dura, and is present from the seventh cervical to the second lumbar vertebra. It contains a quantity of loose areolar tissue, which, in common with similar tissue elsewhere, is slow and ineffective in combating infection. The dura anteriorly is in close apposition to the canal throughout its length. Infection, therefore, is usually found in the dorsal space, except where osteomyelitis of a rib or vertebra, or extension from an extrapleural abscess, is the cause. Once the infection has entered the epidural space rapid spread would be expected, and in most of the published cases the space was widely infected, necessitating removal of many laminae. However, sometimes a circumscribed form of abscess occurs, and it is reasonable to suppose that most cases go through a stage where infection is localized and therefore more amenable to surgery.

Softening of the cord is a common finding in cases which come to necropsy, and it has been suggested that this is due to toxins travelling in by way of the nerve roots, or to ischaemia following on a thrombosis of the vessels, as the changes are much more than can be explained by mere mechanical compression. The organism in the reported cases has been either *Staphylococcus albus* or *Staphylococcus aureus*.

Aetiology

Cases fall into three groups: (1) those where extension from a neighbouring source of infection can be traced; (2) those arising by metastasis from a distant infection; (3) those in which no primary focus can be demonstrated. Trauma is mentioned by several writers as an inciting agent, but it is difficult to prove that it is.

Diagnosis

Diagnosis may present difficulties, but writers are unanimous in stressing the appearance of early and persistent pain localized over the site of the abscess or radiating along the nerve roots. Temperature varies, but