STREPTOCOCCAL INFECTIONS

EDITED BY

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STREPTOCOCCAL INFECTIONS

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Preface

THE GENERAL PLAN of organization of this symposium is more or less obvious from the list of titles included in the table of contents. The symposium begins with a consideration of certain aspects of the biology and chemistry of hemolytic streptococci, primarily those of group A, and proceeds to problems concerned with the interrelationship between the organism and the host. Discussion of the host reaction to group A streptococci naturally leads up to, and is intimately involved in, the practical clinical aspects of streptococcal disease. Finally, following the papers dealing with several phases of streptococcal infection, attention is turned to the important sequelae which follow in the wake of these infections.

No attempt was made to provide completely comprehensive coverage of all facets of the subject, nor would it have been possible without undue expansion of the symposium. It will be immediately evident, for example, that certain of the extracellular products of group A streptococci, such as the erythrogenic toxin, streptococcal hyaluronidase, and streptococcal desoxyribonuclease, do not receive detailed treatment in individual papers. In some instances, omission of a topic was dictated by the lack of sufficient material to warrant its consideration as an independent unit, and in others, as in the case of hyaluronic acid and hyaluronidase, the omission was in recognition of inclusion of the subject in a recent extensive and general symposium on these substances. The topics selected are meant to provide representative examples of the diverse potentialities of hemolytic streptococci in the production of biologically active substances. In another area, it will be recognized that, in view of the relative importance of the subject, discussion of the post-streptococcal diseases is highly restricted. However, the aim here was to stress certain of the more important recent developments, and for broader treatment of the many problems involved one can turn to the recently published monograph on rheumatic fever based on the symposium held at the University of Minnesota.

It is regretted that the last paper of the symposium entitled, "The relative effectiveness of ACTH, cortisone, and aspirin in the treatment of rheumatic fever," by Dr. David D. Rutstein could not be published in this volume. This paper gave a summary of the results of the international study organized by the Council for Rheumatic Fever and Congenital Heart Disease of the American Heart Association. The results of this cooperative study will be published simultaneously in Great Britain and the United States in the near future.

To a large extent, it will be necessary for the reader to supply his own transitions and integrations in passing from one subject to another. However, it is hoped that the interrelationships between the extensive basic knowledge of the hemolytic streptococcus, the pattern of host response, and the manifestations of streptococcal disease have been made apparent in the course of the symposium.

MACLYN MCCARTY

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Chapter 1

CELLULAR CONSTITUENTS OF GROUP A STREPTOCOCCI CONCERNED IN ANTIGENICITY AND VIRULENCE

By Rebecca C. Lancefield, *Hospital of The Rockefeller Institute for Medical Research*

I shall limit my remarks to group A hemolytic streptococci, because they are of major importance in human streptococcal infections. The constituents of group A streptococci to be discussed are listed in Table 1. They are cellular components concerned in antigenicity and virulence.

GROUP-SPECIFIC C CARBOHYDRATE

Group A streptococci are characterized serologically by the presence of a specific polysaccharide, the so-called C carbohydrate (1). This polysaccharide is easily obtainable in soluble form when either the streptococcal cell or the cell wall residues are hydrolyzed by acid, or dissolved with strong alkali, or lysed enzymatically with culture fluids of *Streptomyces albus,* as described originally by Maxted (2). The investigations of both McCarty at the Rockefeller Institute and Salton in Cambridge, England, indicate that the group-specific polysaccharides of the various serological groups of streptococci so far examined are structural components of the cell wall (3). Furthermore, McCarty has shown that the C carbohydrate is not released in appreciable amounts until after dissolution of the cell wall itself. He has evidence that some part of the polysaccharide molecule as it exists in the cell wall serves as substrate for the lytic enzyme factors of *Streptomyces albus.* His findings with the digestion products resulting from lysis of the cell wall suggest that the C polysaccharide molecule is split enzymatically into fragments of unequal composition. Fractional precipitation of solutions of the polysaccharide with different concentrations of alcohol suggested the same thing since serologically active fractions with different proportions of glucosamine and rhamnose were separated by

TABLE 1

CELLULAR CONSTITUENTS OF GROUP A STREPTOCOCCI CONCERNED IN ANTIGENICITY AND VIRULENCE

Designation	*Serological Reactions*	*Chemical Composition*	*Certain Distinctive Properties*
C	Group-specific	Polysaccharide	Structural component of cell wall. Composed of N-acetyl glucosamine and rhamnose.
M	Type-specific	Protein	Alcohol-soluble. Resistant to heating at pH 2. Destroyed by proteolytic enzymes. Important factor in virulence. M antibodies confer protection.
T	Usually common to several types. Occasionally type-specific.	Protein	Resistant to proteolytic enzymes. Destroyed by heating at pH 2. Resists heating in slightly alkaline solutions.
R	Occurs in type 28 strains and in certain strains of groups B, C, and G.	Protein	Resistant to proteolytic enzymes except pepsin. Destroyed by heating at pH 2. Resists heating at alkaline reactions.
Mucoid capsular substance.	None (Nonantigenic)	Mucopolysaccharide	Occurs in groups A & C streptococci (as well as in many animal tissues).
		Hyaluronic acid	Composed of N-acetyl glucosamine and glucuronic acid. Depolymerized by hyaluronidases. Probably at least 2 enzymes involved. Some relationship to virulence.

this procedure. McCarty pointed out that an alternative explanation might be that the polysaccharide does not occur as a homogeneous substance in the cell wall.

In McCarty's experiments, chemical analysis of polysaccharide preparations from seven different group A strains representing six different serological types gave ratios of rhamnose to hexosamine of approximately 1.6. Schmidt at Harvard, however, consistently obtained preparations of C polysaccharide by a different method with a higher content of rhamnose, although some of the same strains of group A streptococci were used by both investigators (4). The explanation for these different findings is not at present obvious.

It is of interest that McCarty's study of the streptococcal cell wall led him to the solution of a problem of long standing which he has very kindly suggested that I include in this review, although this work is not yet published (5). He has discovered the nature of the change in occasional streptococci which no longer produce the serologically active group-specific C polysaccharide characteristic of group A. In 1945 Wilson reported that the stock type 27 strain had, during serial passage through mice, lost its ability to produce C polysaccharide although other specific antigens of the cell remained unchanged (6). Similar findings with two other strains have been reported from this laboratory recently (7). McCarty found that cell wall preparations of these strains although deficient in group A specific polysaccharide nevertheless had as high a content of carbohydrate as the cell walls of the group A strains from which the variants were derived. At first, no method of producing antibodies for the changed polysaccharide could be found. Eventually, however, potent antisera against these variant strains were prepared by digesting the streptococci with pepsin or trypsin before they were used for immunizing rabbits (8). It was then quickly found that all the strains which had lost their group-specific reactivity had substituted a polysaccharide with the same new serological specificity. Chemical analysis of the new polysaccharide from the variant strains showed that, like the original group A polysaccharide, it is composed of rhamnose and acetyl-glucosamine but in different proportions from those found in the C polysaccharide of the parent strains. The ratio of rhamnose to glucosamine in the variant averaged 4.5 instead of 1.6 as found for the original. Current investigations, which will be reported in detail elsewhere, are being carried

out in our laboratory to elucidate the serological and chemical nature of this change, as well as the possible bearing on the epidemiology of streptococcal infections.

TYPE-SPECIFIC M PROTEIN

Serologically specific and distinct polysaccharides have served as an accurate means of separating streptococci from various sources into numerous serological groups, in addition to group A, which are related in a general way to the animal hosts involved (1b). By somewhat similar methods, group A streptococci have been further subdivided into serological types based upon type-specific proteins, the so-called M antigens (9). This has been accomplished by use of several standard immunological methods. Thus, Griffith developed a slide agglutination technique and designated the first 30 types according to the predominant antigen present in strains freshly isolated from human infections (10). In most cases these results were consistent with those obtained in this country in which passive protection tests in mice and the precipitin reaction were used as additional means of analyzing the type-specificities of group A streptococci (11). New types have been identified in various laboratories from time to time since Griffith's original classification was made so that at least 45 specific types are now recognized (12, 19). During the course of this work it became apparent that the protein, M, was the antigen responsible for the type-specific reactions of group A streptococci, whether the method used to demonstrate this specificity was agglutination, the precipitin reaction, or the protection test.

The type-specific M antigen has, for this reason, been the subject of intensive study. Its biological relationships to virulence and protection are now generally accepted. M antigen belongs to the class of alcohol-soluble proteins. Another characteristic chemical property is its resistance to heating at low pH, and it has been shown to withstand a pH of 2 for 20 to 30 minutes in a boiling water bath (9, 13). This antigen is, however, highly susceptible to the action of proteolytic enzymes. Originally thought to be distributed throughout the streptococcal cell body, it was later found to be located entirely at or near the cell surface from which it could be removed by the action of trypsin without killing the cell (8). Grown in the presence of active

trypsin, group A streptococci yield no M antigen, because this protein is destroyed by tryptic digestion immediately after it is formed (14). As soon as the cells are allowed to multiply in the absence of proteolytic enzyme, the usual amount of M antigen is again found in the culture.

Salton has studied cell wall preparations of a strain of group A streptococcus and found that the M antigen remained associated with the cell wall after mechanical disruption of the cells (3b). The behavior of M antigen in these cell wall preparations is analogous to that of M antigen in the intact cell. Thus, a strong type-specific precipitin reaction was obtained with M extracts prepared from cell walls. Treatment of cell wall preparations with trypsin removed and destroyed the M antigen without affecting the content of group-specific C carbohydrate.

Continued attempts to purify the M antigen for study have met with only partial success (13). Recent analysis of type 1 M antigen, purified to a considerable degree but still containing demonstrable impurities, showed that the preparation was almost homogeneous electrophoretically and was isoelectric at pH 5.3. It was free of nucleic acid as shown by the absence of phosphorus and by its ultraviolet absorption spectrum. The sulfur content was 2.46 percent. This protein preparation was antigenic, inducing in rabbits the formation of type-specific precipitins and protective antibodies. Findings of a similar nature with strains not identified as to type have also been described in Mudd's laboratory (15).

NON-TYPE-SPECIFIC T PROTEIN

During the course of experiments designed to correlate the results obtained by means of type-specific agglutination with the results of active or passive protection of mice, another protein antigen associated with agglutination was encountered (16). At first it was thought that this antigen was a second type-specific substance with a distinct serological specificity and that it usually occurred in association with the corresponding M antigen. Accordingly it was designated as the T antigen to denote its relationship to type-specificity. This nomenclature was a mistake, for it soon developed that, although T antigens occur in most strains of group A streptococci, their distribution is inde-

pendent of the distribution of the recognized type-specific M antigens. Furthermore, although T antigens do have a prominent role in agglutination reactions, they have no demonstrable relationship to virulence nor have their antibodies been shown to participate in protection.

TABLE 2

ANTIGENS CONCERNED IN TYPE-SPECIFIC REACTIONS OF GROUP A STREPTOCOCCI

Type	*Antigenic Composition*		*Examples of Some of the Known Antigenic Variants*		
1	M 1 T 1		1) M 1, T 1 2) M 1 3) T 1 4) Neither		
2	M 2 T 2		1) M 2, T 2 2) T 2		
3	M 3 T 3		1) M 3, T 3 2) M 3, T 3, T 1 (Strain C203)		
15	M 15	One or more common T antigens	1) M 15 2) M 17 3) M 23	One T factor common to these 3 types	One T factor common to all 6 types
17	M 17				
19	M 19		4) M 19 5) M 30	Another T factor common to these 2 types	
23	M 23				
30	M 30				
47	M 47		6) M 47		
12	M 12 T 10 or T 12		1) M 12, T 10 2) M 12, T 12 3) T 10 4) T 12		

Examples of the relative distribution of M and T antigens are shown in Table 2. The types of group A streptococci are designated according to the M antigen of the strains and correspond, with one exception, to those established by Griffith on the basis of slide agglutination

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