Current Problems in Studies of Streptococci

Second Griffith Memorial Lecture

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A brief synopsis of the full lecture.

‘To bacteriologists Dr Fred Griffith is universally known for his fundamental work of type transformation in pneumococci and for his studies on the classification of the haemolytic streptococci (Griffith, 1928). He early developed a new method of slide agglutination which he used with success on pathogenic streptococci isolated from infections in man. In 1934 he published a study of the first 27 types (Griffith, 1934). Precipitin reactions with the M antigen were the basis of studies in my laboratory of the serological types of haemolytic streptococci (Lancefield, 1928). Dr Griffith and I exchanged strains and sera and found that with very few exceptions we agreed on the typing results. The number of types has now risen to 55. In this second Griffith Memorial Lecture some of the significant advances in streptococcal research since 1941 are reported.

‘It was found that a second antigen, designated T, stimulated antibodies which reacted in slide-agglutination tests (Lancefield, 1940). The specificity of the T antigen did not always agree with that of the M antigen (Lancefield, 1954). Some strains isolated from impetigo were classified by slide agglutination into the three main T-antigen patterns by Parker and others in 1955 (Parker, Tomlinson & Williams, 1955; Barrow, 1955). However, these strains gave no recognizable M-precipitin reaction. Identification of these strains was important because impetigo is often associated with acute glomerulonephritis. Search for previously unrecognized M-types among pyoderma strains uncovered at least four new types, two of these from acute glomerulonephritis (Anthony, Perlman & Wannamaker, 1967). It is now known that certain M-type infections with some strains are followed by epidemic glomerulonephritis, and infections with other strains of the same type occur in streptococcal epidemics unassociated with nephritis. Five or six types are now generally accepted as including nephritogenic strains (Johnson, Baskin, Beachey & Stollerman, 1968). Attempts to isolate a toxin, or other substances of significance in glomerulonephritis, from nephritogenic strains have been unsuccessful.’

The Lecturer next discussed a few selected examples of immunological studies of the antigenic composition of group A streptococci, representing the trend of streptococcal research in recent years. The isolation and analysis of the streptococcal cell wall (Salton, 1952) and the localization of many antigenic components were stressed (McCarty, 1964). These studies showed that the mucopeptide is the only structural component of the rigid streptococcal cell wall left after removal of all other substances.

Active groupings of the cell-wall polysaccharides which determine the immunological specificities of many of the serological groups of streptococci have been established. This work has been greatly aided by specifically induced enzymes from soil bacilli.

Renewed interest in purifying the type-specific protein M-antigen of group A streptococci has been stimulated by the development of new biochemical methods for purification. This may make active immunization of rheumatic fever subjects possible, instead of protecting them from streptococcal infections by the use of chemoprophylaxis, as is the current practice. By using purified M preparations, Fox and colleagues have obtained bactericidal antibodies in infants with few or no side reactions (Fox, Wittner & Dorfman, 1966). It is not known, however, whether this anti-M immune response in the absence of an infection is a reliable index of type-specific immunity.

The possibility of danger to the patients from immunological cross-reactions between the streptococcal products injected and cardiac tissues of rheumatic-fever subjects has received much consideration due to studies of such cross-reactions by Kaplan (1963), by Zabriskie (1967), by Goldstein, Halpern & Robert (1967). In contrast to the possible dangers of active immunization is the fact that so far there is no indication that any of these cross-reactive antibodies actually cause cardiac lesions, despite many previous attempts to immunize man with a variety of streptococcal products.

Of the many important extracellular products of group-A streptococci, brief mention was made only of a few. The early studies of Dr Edgar W. Todd on streptolysin-O have been followed by the universal use of his test for the presence of anti-streptolysin-O, as indicative of a preceding streptococcal infection (Todd, 1938). Todd also introduced to streptococcal work the bactericidal test used today almost exclusively to measure in man the anti-M antibodies upon which type-specific immunity depends (Todd, 1927).

One of the most interesting and well-studied streptococcal systems is the proteinase and its precursor. This enzyme and its zymogen have been crystallized and extensively studied by Elliott (1950) and by other biochemical colleagues. These enzymes are of special interest to enzyme chemists because both zymogen and active enzyme contain only one-half cystine residue per molecule (Liu *et al.* 1963, 1965).

Another especially interesting extracellular product is the erythrogenic toxin. Zabriskie (1964) has shown that only strains infected with temperate bacteriophage are toxin producers.

In reviewing examples of the known array of streptococcal antigens, too many to be discussed here, it seems apparent that very few bacterial species have as much known about their chemical composition and immunochemical properties as the streptococci, which have been studied by so many different investigators.

REFERENCES

- ANTHONY, B. F., PERLMAN, L. V. & WANNAMAKER, L. W. (1967). Skin infections and acute nephritis in American Indian children. *Pediatrics, Springfield*. **39**, 263.
BARROW, G. I. (1955). Clinical and bacteriologic aspects of impetigo contagiosa. *J. Hyg., Camb.* **53**, 495.
ELLIOTT, S. D. (1950). The crystallization and serological differentiation of a streptococcal proteinase and its precursor. *J. exp. Med.* **92**, 201.

- FOX, E. N., WITTNER, M. K. & DORFMAN, A. (1966). Antigenicity of the M proteins of group A, streptococci. III. Antibody responses and cutaneous hypersensitivity in humans. *J. exp. Med.* **124**, 1135.
- GOLDSTEIN, I., HALPERN, B. & ROBERT, L. (1967). Immunological relationship between streptococcus A polysaccharide and the structural glycoprotein of heart valve. *Nature, Lond.* **213**, 44.
- GRIFFITH, F. (1928). The significance of pneumococcal types. *J. Hyg., Camb.* **27**, 113.
- GRIFFITH, F. (1934). The serological classification of *Streptococcus pyogenes*. *J. Hyg., Camb.* **34**, 542.
- JOHNSON, J. C., BASKIN, R. C., BEACHEY, E. H. & STOLLERMAN, G. H. (1968). Virulence of skin strains of nephritogenic group A streptococci: new M protein serotypes. *J. Immun.* **101**, 187.
- KAPLAN, M. H. (1963). Immunologic reaction of streptococcal and tissue antigens. I. Properties of an antigen in certain strains of group A streptococci, exhibiting an immunologic cross reaction with human heart tissue. *J. Immun.* **90**, 595.
- LANCEFIELD, R. C. (1928). The antigenic complex of *Streptococcus haemolyticus*. I. Demonstration of a type-specific substance in extracts of *Streptococcus haemolyticus*. *J. exp. Med.* **47**, 91.
- LANCEFIELD, R. C. (1940). Type-specific antigens, M and T, of matt and glossy variants of group A haemolytic streptococci. *J. exp. Med.* **71**, 521.
- LANCEFIELD, R. C. (1954). Cellular constituents of Group A streptococci concerned in antigenicity and virulence. In *Streptococcal Infections*. Ed. by M. McCarty. Chap. 1, p. 3. Columbia University Press.
- LIU, T. Y., STEIN, W. H., MOORE, S. & ELLIOTT, S. D. (1965). The sequence of amino acid residues around the sulphhydryl group at the active site of streptococcal proteinase. *J. biol. Chem.* **240**, 1143.
- LIU, T. Y., NEUMANN, N. P., ELLIOTT, S. D., MOORE, S. & STEIN, W. H. (1963). Chemical properties of streptococcal proteinase and its zymogen. *J. biol. Chem.* **238**, 251.
- MCCARTY, M. (1964). The streptococcal cell wall and its biologic significance. In *The Streptococcus Rheumatic Fever and Glomerulonephritis*. Baltimore: Williams and Wilkins Company.
- PARKER, M. T., TOMLINSON, A. J. H. & WILLIAMS, R. E. O. (1955). Impetigo contagiosa: the association of certain types of *Staphylococcus aureus* and of *Streptococcus pyogenes* with superficial skin infections. *J. Hyg., Camb.* **53**, 458.
- SALTON, M. R. J. (1952). The nature of the cell walls of some Gram-positive and Gram-negative bacteria. *Biochim. biophys. Acta* **9**, 334.
- TODD, E. W. (1938). The differentiation of two distinct serological varieties of streptolysin, streptolysin O and streptolysin S. *J. Path. Bact.* **47**, 423.
- TODD, E. W. (1927). A method of measuring the increase or decrease of the population of haemolytic streptococci in blood. *Br. J. exp. Path.* **8**, 1.
- ZABRISKIE, J. B. (1964). The role of temperate bacteriophage in the production of erythrogenic toxin by group A streptococci. *J. exp. Med.* **119**, 761.
- ZABRISKIE, J. B. (1967). Mimetic relationship between Group A streptococci and mammalian tissues. *Adv. Immun.* **7**, 147.