Tracking the Identity of Lister's Pneumococcal Groups T and V (Danish Types 45 and 46)

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An historical account is presented of attempts to establish the serologic identity of Lister's pneumococcal capsular Groups T and V.

Intimations of the serologic diversity of pneumococci, isolated independently in 1880 by Sternberg and by Pasteur, began to appear shortly before the end of the nineteenth century. In June 1897, Bezanson and Griffon [1], attempting to devise an analogue of the Widal test to be used in the diagnosis of pneumococcal infection, described the pneumococcal agglutinating capacity of sera derived from experimentally infected animals and from naturally infected humans. For their test organism, they used a strain of pneumococcus recovered in December 1896, from the heart's blood of a mouse inoculated with sputum from a man with pneumonia. In all, Bezanson and Griffon studied the sera of seven patients with pneumonia. The sera of five patients agglutinated their test strain of pneumococcus; but those of two cases, one with a necrotizing pneumonia and the other with purulent pleurisy of long duration, failed to do so. The organism recovered from the case of necrotizing pneumonia had some attributes similar to those of pneumococcus type 3. Of the two latter cases, the authors wrote: “In these two cases, the absence of the agglutinating reaction in the serum seeded with the common pneumococcus ('le pneumocoque vulgaire') permits us to see that, besides the common pneumococcus, there exist some other races of pneumococcus, which, from the point of view of agglutination, behave as different microbes.” They concluded that these findings, plus the difficulty in culturing pneumococcus, made it unlikely that serodiagnosis could be applied to the diagnosis of pneumococcal infection as it is in the diagnosis of typhoid fever.

In the ensuing 13 years, additional observations suggesting the heterogeneity of pneumococcal types appeared, culminating in the report of Neufeld and Händel, which established this fact in 1910 [2]. The history of this period has been reviewed both by White [3] and by Heffron [4].

In 1911, Sir Almroth Wright, who is usually credited with the development of typhoid vaccine, went from England to South Africa to attempt to reduce by prophylactic inoculation the ravages of pneumococcal pneumonia among gold miners in that country [5]. Although Neufeld and Händel's report indicating the existence
of at least two serotypes of pneumococcus had appeared the year before, there is no indication in the publications of Wright and his colleagues that cognizance was taken of this fact in the preparation of the pneumococcal vaccines employed in the initial field trials. Among Wright's associates in these investigations was F. Spencer Lister [6].

Frederick Spencer Lister was born in Nottinghamshire, England, in 1875. He was educated in Cambridgeshire and, after attending St. Bartholomew's Hospital, qualified as M.R.C.S. in 1905. Thereafter, he served for a time as the doctor aboard a cable-laying ship and arrived in South Africa in 1907. Electing to remain in that country and following a brief period in private practice, he became associated with the mining industry. There he developed an interest in pneumonia which led to his association with Wright when the latter came to Johannesburg. It was an association that stimulated Lister's continuously productive investigations of the pneumococcus over the ensuing quarter century.

In his early studies with Wright, Lister was struck by the infrequency with which recently isolated strains of pneumococci were opsonized, even with serum of the patient from whom they were recovered. Reasoning that serum obtained at the time of crisis might opsonize the organism causing illness, Lister took isolates from blood or from material obtained by lung puncture and examined the immunologic responses in 20 cases of pneumonia meeting these criteria. Among the 14 cases which recovered, opsonization and agglutination by the patient's serum of the pneumococci causing infection were observed in 12, whereas among the six who died, these phenomena were noted only in two [7]. There are several explanations for the probable failure to detect opsonins in the blood of most patients who died. Death may have occurred sufficiently early in illness to have provided too little time for antibodies (opsonins) to have developed; they are not usually detectable in the serum until a week or more has elapsed following the onset of illness. Second, the patient may have absorbed in the course of severe illness sufficient bacterial capsular antigen to combine with all the antibody (opsonin) produced by the patient; free antibody following recovery from pneumococcal pneumonia may not be detectable in some patients for four to eight weeks after onset of illness.

When the isolates from 18 cases of pneumonia obtained from blood or direct aspirates of the lung were examined systematically with each of the reactive sera, it became quickly apparent that the organisms were serologically heterogeneous, falling into four groups which Lister designated A, B, C, and D. Lister concluded the discussion of his findings with the following remarks:

If the validity of this method of classifying pneumococci be confirmed it will have more than one useful application. The possibility of identifying the particular strains of this organism will provide a clue as to the source of infection in different cases, and will help to elucidate the role of those pneumococcal organisms which are found so commonly in the throats of healthy individuals. The prevalence of different groups of pneumococci in different circumstances—industrial, tribal, geographical etc.—will be capable of investigation. The suggestion that second attacks of pneumonia are due to invasion by another organism can be put to the test. These and many similar enquiries may be rendered feasible.

The prophylactic pneumococcal vaccine now so extensively used on these fields may, in the light of these studies become modified; it is obvious that the efficacy of such vaccine would be enhanced if use were made of the particular
strain of organism to infection by which the labourers will be exposed. It may also be found advantageous to use certain definite combinations of strains. . . .

The serum therapy of pneumonia, which has not hitherto afforded notable results, may derive additional importance when it can be used in so specific a manner as the results of these investigations lead me to hope.

Lister's report coincided closely with one describing studies conducted independently at the Rockefeller Institute, and his text bears the following postscript:

Since committing the above to paper my attention has been drawn to some recent work by A.R. Dochez and L.J. Gillespie and which has appeared in the Journal of the American Medical Association for September 6th, 1913 (pages 727-730). Although these workers have adopted different methods of investigation, yet their observations seem to have led them to conclusions somewhat similar to my own.

Over the ensuing two decades the number of pneumococcal groups identified in South Africa expanded gradually from the four defined in the initial report of 1913 to seven in 1916 [8], 10 in 1917 [9], 15 or 16 in 1931 [10], and 21 in 1935 [11], all designated by capital letters. In the same period, the serotypes of pneumococci classified originally in Dochez and Gillespie's Group IV were scrutinized in a number of laboratories in North America and in Europe, culminating in the publications of Cooper and her associates, who, by 1931, had recognized 33 capsular serotypes of pneumococci [12]. It is of historical interest to note that this immunologic classification of an encapsulated organism was accomplished without utilization of the Quellung reaction, described originally by Neufeld in 1902 [13].

In 1938, David Ordman, an associate of Lister, published a report entitled: "Pneumococcus Types in South Africa. A Study of their Occurrence and Distribution in the Population and the Effect Thereon of Prophylactic Inoculation" [14]. In it, there is a reconciliation of the South African and American designations of pneumococcal types. Of 30 American capsular types (types 26 and 30 were considered identical with types 6 and 15), all but those numbered 31 and 32 had been recognized in South Africa. Of the 30 designated South African Groups (types), all but Groups T and V had their counterparts in Cooper's classification. It should be noted that pneumococci in South African Groups (types) D, F, G, H, J, L, and P were not available for study and that supplies of antiserum to these groups had been exhausted, so that it was no longer possible to determine their identities in other schemes of classification. The table reconciling Lister's and Cooper's nomenclatures may be found in Appendix B of Heffron's monograph [4].

Pneumococcal Groups T and V are cited for the first time in Lister and Ordman's publications in 1935 [11], and the incidence of infection with the former was evidently great enough to lead to its inclusion in the polyvalent whole bacterial vaccine used for the prevention of pneumonia at that period. In Ordman's study of 879 pneumococcal isolates from unvaccinated native Africans with pneumonia, strains of Group T ranked seventh in frequency, accounting for 1.4 percent of all isolates, and those of Group V ranked eighth, together with types 5 and 8, each accounting for 1.1 percent of the strains recovered. Regrettably, no data on bacteremic illness are provided. Among 170 Europeans with pneumonia, pneumococcus Group T was recovered from one, and there were two isolates of capsular Group V [14].
Work on the delineation of additional pneumococcal types continued in the 1940s, both in Denmark and in the United States, and included studies of unclassified strains provided to laboratories in both countries by Ordman. In 1944, Eddy reported that pneumococci of South African capsular Group T, a strain of which she had received from Ordman, were identical with her strain of capsular type 72 in the American classification [15]. Six years later, Lund, in Denmark, published a report entitled “Four New Pneumococcus Types” among which are included Danish capsular types 45 and 46 [16]. Of these types she wrote:

From Dr. Ordman, Johannesburg, South Africa, we have received 3 pneumococcus strains—X4803, X2368, and W5019—that all give capsular swelling in type 45 serum. . . . Type 45 appears to be of rather frequent occurrence in South Africa, whereas it has not yet been demonstrated in Denmark.

Type 46

In 1938 Ordman reported the pneumococcus types found in South Africa. In America, these types were compared with Cooper's types (1-32). For the type designated by Ordman as “T”, no corresponding type was at that time found in the American classification given by Cooper. Subsequently, Eddy (1944) set up “T” as type 72 (group 5).

Type “T” is of rather frequent occurrence in South Africa. Ordman found it in 1.2% of 1496 pneumonia patients and in 1.0% of 693 patients with pneumococcus meningitis. Strain “T” No. 378 was kindly sent us by Dr. Ordman who states that this strain was isolated by him in 1937 from a native miner with pneumonia.

Type “T” is not identical with any of the 73 pneumococcus types hitherto known in Denmark. . . .

Lund's observations pose a curious dilemma; for, by identifying pneumococci of South African Group (type) T with Danish capsular type 46 (American type 73), she is associating pneumococci of Group T with a different capsular type than Eddy, who identified them as belonging to American type 72 (Danish type 45). Commenting on the discrepancy seven years later, Lund stated:

By cross-absorption Eddy’s type 72 is found to be identical with type 45 (Lund, 1950). . . . The strains concerned of type 45 and Eddy 72 were all slightly virulent for mice.

Cross-absorption of Eddy’s type 73 shows identity with type 46 (Lund, 1950). Either strain reacts with type 44. Type 46 is identical with Type T which was established in South Africa by Ordman (1938). Eddy is mistaken when she declares her type 72 identical with type T (Eddy, 1944, p. 450). Type 46 (strain “T”) and Eddy’s strain 73 are both highly virulent for mice [17].

It is clear that there is an unreconciled disagreement between Eddy's and Lund's classification of pneumococci of South African Group (type) T in the Danish and American nomenclatures of capsular types. Interestingly, there is no mention in any of the reports cited of pneumococci of South African Group V, a serotype found with a frequency only slightly less than that of Group T.

In November 1974, in the course of the field trials of pneumococcal vaccine being conducted then in South Africa [18], an attempt was made to locate strains of
pneumococci in groups classified by Lister which had never had their correlates in the contemporary nomenclatures of capsular types established. This search was unsuccessful; but, in the repository of Dr. Ordman's biological reagents at the South African Institute for Medical Research, several sealed ampuls of pneumococcus Group V antiserum were discovered. Two ampuls were taken to the University of Pennsylvania, and the serum was tested systematically with the Quellung reaction against a variety of pneumococcal capsular types. It reacted strongly, despite the fact that it was several decades old, with strains of pneumococcus type 46 in the Danish classification, type 73 in the American scheme. This observation was compatible with Eddy's findings but not with those of Lund, who found Ordman's type T to correspond with Danish type 46.

In 1976, two of Ordman's pneumococcal strains were obtained from Dr. Eddy, who wrote as follows: "The T strain (same as my Type 72) was marked JK: the other culture (same as my type 73) was marked 108E." Strain JK is indeed a strain of type 72 in the American classification (type 45 in the Danish), and strain 108E reacts both with antiserum to capsular type 73 in the American (type 46 in the Danish) classification and with Ordman's antiserum to capsular Group V. It would appear that, somewhere in the interchange of strains among the laboratories in Africa, Europe, and North America, a strain was mislabeled; and it may never be possible to determine with certainty the identity of Lister's pneumococci in Groups T and V. It is most likely, however, that they are represented by types 45 and 46 in the contemporary Danish classification and that type 45 represents Group T and type 46 Group V.

Nearly four decades after Ordman's reconciliation of the South African nomenclature of pneumococcal groups with Cooper's classification of capsular types, pneumococci in Groups T and V, which will be referred to hereafter respectively as types 45 and 46 in the Danish nomenclature, were still prevalent in populations of Southern African gold miners. Among 575 isolates from respiratory secretions and/or blood of patients with radiologically confirmed pneumonia or bacteremia, 63 (11 percent) were type 46 and 14 (2.4 percent) were type 45. Among 189 strains isolated from blood cultures, there were 17 (9 percent) each of types 45 and 46, placing both among the five types most frequently causing bacteremia. Most of the individuals from whom these isolates were obtained were young adult African males from Mozambique or Malawi. None had received pneumococcal vaccine.

Pneumococcal types 45 and 46 are uncommon in most other parts of the world in which studies have been done, although both have been recognized in Papua-New Guinea where type 46 was responsible in one area for 29 (25 percent) of 115 bacteremic infections [19]. In the United States, there were only two isolates of type 45 and three of type 46 among 4,335 pneumococcal strains recovered from blood cultures in the past two decades [20]. Whether or not there is a genetic predisposition to infection with these two pneumococcal types in certain ethnic groups in Southern Africa and in Papua-New Guinea is unknown, although a relationship between human genotype and susceptibility to infection with certain capsulated bacteria has been suggested, but not established, by several groups of investigators [21,22]. The structure of the capsular polysaccharides of pneumococcal types 45 [23] and 46 [24] has each been established recently, information which may be helpful in understanding ultimately their infectivity, and both polymers have been incorporated in experimental vaccines. The work begun by Lister and his associates 70 years ago in South Africa continues to bear fruit.
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