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Of man and pneumococcus, an historical paradox

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In the fifty years spanning the scientific career of André Lwoff, few organisms have played a larger role than has pneumococcus in contributing to the understanding of bacterial disease and of the biology of the cell. Historically it serves as a link between France and the United States, having been described for the first time in the year 1881 by Pasteur in Paris and by Sternberg in New York. It was not until several years later, however, that its importance as the major cause of bacterial pneumonia in man was established by Fraenkel (1884) and by Weichselbaum (1886). Writing of pneumonia at the turn of the century, Osler (1909), in his epochal textbook entitled *The Principles and Practice of Medicine,* designated it "Captain of the men of death."

Study of the causative organism of a disease of such importance, which strikes down the young as well as the aged, was bound to be intense. How else could a rational approach to therapy be achieved? The initial attempts to produce an effective antiserum in a fashion analogous to that employed so successfully for diphtheria antitoxin failed to meet with success, for the serologic diversity of pneumococcus had not been recognized. Only after three distinct serotypes and an heterogenous collection of strains categorized as Group IV (Dochez and Gillespie, 1913) had been identified was an approach to the serotherapy of pneumonia possible. The beneficial effect of Type I antipneumococcal horse serum was established between 1910 and 1920.

As a result of the foregoing investigations, it had become apparent that the capsular antigens of the pneumococcus played a major role in the virulence of the organism and were responsible for its antigenic diversity. Biochemical study of these capsular substances led to the discovery that they are complex polysaccharides (Heidelberger and Avery, 1923) and to the milestone in immunology that molecules other than proteins can stimulate the formation of antibodies. Attempts to define better the conditions determining reacquisition by avirulent pneumococci of the ability to produce a capsule resulted in the first demonstration of bacterial transformation by Griffith (1928). Although the significance of Griffith's findings was not appreciated fully at the time, they were to prove to be the initial step in the establishment of deoxyribonucleic acid as the major biochemical determinant of heredity (Avery, MacLeod, and McCarty, 1944). These observations serve well to illustrate the "fallout" of fundamental biological knowledge resulting from the study of an important pathogen of man.

Meanwhile, further progress was being made in the classification of pneumococcal capsular types and in the production of sera to treat pneumococcal disease. Definition of 32 serotypes by Cooper and her associates (1929) and the substitution of rabbit antisera for those produced in horses marked the next steps in the efforts to provide effective therapeutic measures for the management of pneumonia. Despite these advances, the era of serotherapy was nearing its end. In 1935, Domagk reported the initial use of a sulfonamide in the treatment of a bacterial infection; and, in 1938, Whitby described the successful employment of sulfapyridine for the therapy of pneumococcal disease. For the first time, treatment of pneumococcal infection, regardless of the capsular type of the causative organism, was possible with a single chemotherapeutic agent.

Although the death rate from pneumonia in the United States had begun to fall at the beginning of the twentieth century and had continued to do so except in the years of the influenza pandemic of 1918–1919, the total number of deaths from pneumonia continued at a significant level as a result of the steady growth of the nation's population. No more than a slight effect of serum therapy on the death rate from pneumococcal disease can be observed, a not too surprising finding in view of the fact that such treatment was generally available for the

management of infections caused by only a few capsular types. Since sulfonamides are potent against pneumococcus regardless of type, their impact on the death rate from pneumonia, following their widespread introduction in 1938, is clearly evident. Fear of the potentially fatal outcome of pneumococcal infection and the lower but continuing significant death rate accompanying sulfonamide therapy led for a time to retention of the highly efficient laboratory techniques for the isolation and typing of pneumococci and, on occasion, to the treatment of the seriously ill with both sulfonamides and type-specific antipneumococcal serum. The advent of penicillin, however, was soon to bring about marked changes in the diagnostic procedures employed in the management of pneumonia and in medical attitudes regarding its prognosis.

The successful treatment of pneumococcal pneumonia with penicillin was reported by Tillet and his associates in 1945. Employing doses that are miniscule by today's standards, they achieved highly satisfactory results. Resembling the sulfonamides in its potency against pneumococci of all capsular types, penicillin differed from the former drugs in being bactericidal rather than bacteriostatic and in manifesting significantly lesser toxicity. To many physicians, it appeared that the battle to control and, perhaps, even to eliminate pneumococcal disease had been won.

The clear superiority of penicillin over all forms of treatment for pneumococcal infection available previously led quickly to cessation of the production of therapeutic type-specific antipneumococcal sera. Diagnostic pneumococcal typing sera, by-products of therapeutic sera, became decreasingly available; and, by the early 1950's, no commercial source of such diagnostic reagents could be found in the United States. For more than a decade, their only commercial source in the Western world has been the Statens Seruminstitut, Copenhagen, Denmark. For the identification of pneumococcus in clinical laboratories, reliance was placed on bacterial cellular and colonial morphology, the solubility of the organism in bile salts, and its sensitivity to ethylhydrocupreine hydrochloride. None of these tests permitted the identification of pneumococcus with the speed or accuracy of the capsular precipitin or *Quellung* reaction. Neither did they permit the useful prognostic inferences that could be drawn from knowledge of the capsular type of pneumococcus responsible for infection.

With the abandonment of time-tested methods, the frequency and accuracy with which pneumococcus was recognized in the clinical laboratory declined rapidly. These changes are reflected in the medical writing of the period. In 1950, Reimann wrote: "Unfortunately, since the determination of types of pneumococci which cause pneumonia is no longer of practical necessity for therapy, the procedure has been almost entirely abandoned." Six years later, this view was echoed by Rhoads (1956): "A revealing sign of the times is that no efforts were made at typing pneumococci in the entire series, for specific antiserum has not been used at this hospital for many years." An even more nihilistic outlook is found in the statement of Bridge in 1956: "In cases of pneumonia in the age group 15–60 without significant coexistent disease, it is felt that routine bacteriologic studies are unnecessary." The situation with regard to pneumococcal typing in Great Britain would appear to be similar to that in the United States, for an editorial on pneumococcal pneumonia published in *Lancet* in 1968 states: ". . . so far as we know, no one types them [pneumococci] routinely."

At the same time that penicillin was undergoing its initial trials in the treatment of pneumococcal disease, prevention of such infection was under scrutiny elsewhere. In an effort to reduce the loss of manpower caused by epidemic pneumococcal pneumonia in an army air force training school, MacLeod and his associates (1945) immunized 8500 men against four of the six pneumococcal types responsible for the epidemic disease. A similar group of men served as controls. The vaccine consisted of 50 μg each of the purified capsular polysaccharides of pneumococcal types I, II, V, and VII. Immunization was not provided against the other two epidemic types, IV and XII, which served as controls in both groups. The results of the vaccine trial showed clearly that infection caused by the pneumococcal types included in the vaccine could be prevented by immunization with them. The study suggested also that, in a closed population such as the one under investigation, the presence of immunity in half the group impeded the spread of epidemic strains through the population with a resultant lowering of the incidence of the disease in the controls. The effects of the vaccine were quite specific, for there was no reduction in the incidence of disease caused by pneumococcal types other than those included in the vaccine in either segment of the population.

That pneumococcal vaccine could also prevent infection in an older population was reported several years later by Kaufman (1947), who demonstrated a 90% reduction in the incidence of pneumonia and of bacteremia caused by pneumococcal types I, II, and III in a controlled study involving 10,000 persons 50 years of age or older, half of whom received vaccine. Further studies of vaccines of purified pneumococcal capsular polysaccharides showed that, when 50 μg each of six different polysaccharides were administered simultaneously, most subjects manifested an antibody response to all six (Heidelberger, MacLeod, and DiLapi, 1948); that half-maximal levels of antibody persisted as long as 5–8 years after a single injection of capsular polysaccharides (Heidelberger, 1953); and that injection of the vaccine was followed by a rate of untoward reactions considerably lower than that following the administration of typhoid vaccine. For that definable segment of the population at high risk of infection and of death caused by the commoner and more invasive pneumococcal types, the polyvalent vaccine of purified capsular polysaccharides would appear to have possessed the attributes of a highly satisfactory prophylactic agent.

Although licensed for commercial production after World War II, pneumococcal vaccine became available at that historical point in time when the medical profession had become convinced that pneumococcal disease was no longer a significant problem, and use of the vaccine was negligible. It was withdrawn from the market in the early 1950's; and, at the same time, the manufacturer asked that the license for its production be revoked without prejudice.

The foregoing historical notes delineate an extraordinary paradox. Having obtained, after years of intensive search, the means to treat effectively or to prevent a common infection with a significant fatality rate, the medical profession abandoned forthwith the technique of diagnosing it accurately. Failure to recognize pneumococcus in the hospital laboratory led soon to the widely held view that pneumococcal disease had become a rarity and to the impression, for example, that only three or four cases of pneumococcal pneumonia were being admitted annually to the 3000 bed municipal hospital of a large urban area.

To determine whether or not prevailing concepts concerning the incidence and severity of pneumococcal disease and the distribution of

infecting pneumococcal types were indeed true, a laboratory was established in 1952 to serve a large urban medical service to which previously untreated patients were admitted in large numbers, including those ill with pneumonia. Cultures of respiratory secretions and of blood were obtained routinely before the administration of antimicrobial agents and were examined by previously established techniques for the isolation of pneumococcus. All strains of bacteria isolated which resembled pneumococci were typed by the capsular precipitin or *Quellung* technique.

The results of this investigation of pneumococcal infection (Austrian and Gold, 1964) established a number of facts:

1. That 20–25 bacteremic pneumococcal infections were observed annually for each 100–125 medical ward beds, an incidence similar to that seen before the advent of antibiotics.
2. That nonbacteremic pneumococcal pneumonia continued to occur with a frequency 3–4 times that of bacteremic infection.
3. That, with the exception of capsular Type II, the types of pneumococcus responsible for bacteremic pneumococcal infection were the same as those causing such infections before antibiotics were available.
4. That the fatality rate resulting from bacteremic pneumococcal pneumonia treated with penicillin or with other antibiotics was 17–18%, and that, in persons 50 years of age or older or in those with underlying systemic illness, the fatality in similarly treated patients exceeded 25%.
5. That the preponderance of deaths occurred in those sustaining irreversible physiologic damage within 5 days of the onset of infection.

The findings indicated clearly that pneumococcal disease is still prevalent, and that, for certain definable segments of the population, such infection is still accompanied by a significant risk of a fatal outcome, a risk unlikely to be lessened by antibacterial therapy alone. Until the mechanisms whereby pneumococcus damages man and the

means to control them are known, the discarded technique of prophylaxis would appear to offer the greatest likelihood of reducing the still significant mortality from pneumococcal infection.

"Pneumonia and influenza" is the only category of infectious disease among the ten leading causes of death in the United States, ranking fifth in 1965. In that year 59,608 deaths were attributed to pneumonia alone (*Statistical Abstract of the United States,* 1967). If an overall mortality rate for pneumonia of 10% is assumed, there were over half a million such illnesses in the same year. In periods when influenza virus is not epidemic, the preponderance of deaths from pneumonia is due to bacterial infection, and at least 80% of these are caused by pneumococcus. In addition to the saving in lives that could be effected by prophylactic vaccination against infection with the more prevalent and virulent pneumococcal types, the reduction in human disability that might result from the prevention of such illness would be appreciable. Because the incidence of pneumonia is higher in the aged, the problems it causes can be expected to increase. In 1966, there were 35,718,000 persons 55 years of age or older in the United States. The number falling into this same age group is projected by the Bureau of the Census (*Statistical Abstract of the United States,* 1967) to increase to 46,214,000 in 1985. It would seem reasonable, in the light of these estimates, to attempt to reduce the cost in lives and in illness brought about by pneumonia by reintroduction of polyvalent pneumococcal vaccine.

To further this end, a program designed to lead to the relicensing of pneumococcal vaccine is currently in progress, supported by the National Institute of Allergy and Infectious Diseases of the U.S. Public Health Service. Surveillance of the pneumococcal types responsible for bacteremic infection has been extended geographically, and more than 1500 bacteremic infections have been identified in nine urban areas of the United States in the last 30 months (Austrian, 1969). Types I, III, IV, VII, VIII, and XII account for 52.5% of such infections.

Surveillance of the incidence of pneumococcal infection in populations of defined size is now also in progress. The development of a radio-immunoprecipitin assay for antibody to pneumococcal capsular polysaccharides (Schiffman, 1969) makes possible for the first time a

rapid and convenient method for measurement of the antibody response to pneumococcal infection in patients with and without bacteremia. Demonstration of such a response is an essential part of establishing the causal role in infection of an organism isolated from sputum.

Vaccine is currently in production. After having been tested for safety and for efficacy in inducing an immune response, it will be assayed for its ability to prevent disease in field trials in the populations in which the incidence of pneumococcal disease has been ascertained previously. If the results are similar to those obtained by MacLeod and his coworkers (1945), as anticipated, vaccine will be made generally available once again.

The medical profession has not been immune to fads in the past, nor is it likely to be so in the future. Significant therapeutic advances are not infrequently accompanied by overoptimism and the hope that a particular disorder can be eliminated completely. This latter goal is rarely, if ever, attained where illnesses of infectious origin are concerned, however, and control of such disorders is more likely to be achieved by immune prophylaxis than by the administration of antimicrobial drugs. Let us not lay ourselves open to the charge of Molière: ". . . et j'ai connu une homme qui prouvait, par de bonnes raisons, qu'il ne faut jamais dire: 'Une telle personne est morte d'une fièvre et d'une fluxion sur la poitrine'; mais: 'Elle est morte de quatres médecins et de deux apothocaires' " (*L'Amour Médecin,* Acte II, Scène I).

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