Leading articles

The need for a pneumococcal vaccine

The exact incidence of pneumococcal disease in the United Kingdom is not known and yet invasive pneumococcal infection causes high morbidity and significant mortality in spite of the introduction of effective antimicrobial agents. Even though antibiotics may be highly effective in eliminating the microbial aspect of pneumococcal disease there is no known means for reversing or negating the physiological damage that is incurred during the first five days of the onset of the illness. Austrian (1977) who has worked with the pneumococcus for almost three decades firmly believes that although the mortality from pneumococcal infection has declined strikingly since the introduction of antibiotics the attack rates of pneumococcal infections have diminished little and until the nature of the physiological injury induced by pneumococcal infection is better understood and the means to correct it instituted it is unlikely that the prognosis of this disease can be improved. This pessimistic but realistic view is supported by Cockburn (1979) who stresses that it is only by controlling respiratory diseases which include pneumococcal infection that any further significant reductions in death rates from infectious diseases can be obtained in the developed world.

The diagnosis of pneumococcal pneumonia is far from exact although the identification of *Streptococcus pneumoniae* is well established. This is because the pneumococcus is part of the normal flora in the upper respiratory tract and its role in infection of the lower respiratory tract is uncertain when it is recovered only from sputum using conventional techniques. Sampling errors are common and difficulties of interpretation are compounded when sputum samples are collected from patients who have been treated with antibiotics (Spencer & Philp, 1973). Other workers (Dulake, 1979) exploited immunological techniques and showed that in spite of chemotherapy pneumococcal antigens could be detected in over 70% of patients with radiological evidence of pneumonia.

Improved cultural and sampling methods (Schreiner & Digranes, 1979) have allowed sophisticated epidemiological studies to be made (Hince & Howard, 1978) which show surprisingly small differences in the prevalence of pneumococci among several countries (Weber & Kayser, 1979). Although the rank order of the known 84 serotypes may differ, 80% of the prevalent types belong to a small group of 14 serotypes. Careful and studious work at the Statens Seruminstitut (Henrichsein, 1979) has led to the introduction of the Danish nomenclature system which is based to a great extent on cross-reactions between different types; the American system is based on new types being given a consecutive number. The pneumococcal typing system is based on differences in the capsular antigens and on the ability of the immune apparatus of the rabbit to distinguish small differences in the chemical composition of the pneumococcal polysaccharide capsule and to produce specific antibodies against each individual serotype.

Interest in pneumococcal vaccines was first documented about 70 years ago (Wright *et al.*, 1914) when attempts were made to modify the high incidence of pneumococcal pneumonia amongst the gold miners of South Africa using a vaccine which consisted of whole pneumococcal cells. Research on the pneumococcus continued, ably pursued during the 1920's and 1930's by Maxwell Finland and maintained by Dr Austrian. Once more, interest has returned to the South African gold miners where recently 6-valent and 12-valent vaccines have been compared in large numbers of high risk miners (Smit *et al.*, 1977). A double blind controlled trial of a 14-valent pneumococcal vaccine carried out on 12,000 natives in the Papua New Guinea Highlands (Riley *et al.*, 1977) showed that in this high risk group the vaccine produced a large fall in morbidity and mortality due to pneumococcal pneumonia caused by the types of pneumonia included in the vaccine.

The antigenic composition of the current 14 valent vaccine is the most complex to date
and comes at a time when the attack rate of pneumococcal disease remains unabated and the mortality approaching 30% in patients over the age of 50 years with underlying disease. The vaccine is formulated so that every 0.5 ml dose contains 50 μg of each of the 14 polysaccharide types and when given subcutaneously or intramuscularly produces a significant antibody response in over 90% of individuals with no altered effect when given with influenza vaccine. Specific antibody response can be detected after about three weeks and immunity is expected to last for at least three years and perhaps for much longer. Reactions to the vaccine are common place but generally mild and of short duration. The vaccine appears to be effective in persons with anatomical or functional splenic deficiency (Ammann et al., 1977) but there is a lowered antibody response in immunosuppressed patients especially patients with Hodgkin's under extensive chemotherapy. Unfortunately, children under the age of two years respond poorly to the majority of the serotypes in the current vaccine and pneumococcal involvement in otitis media would be unlikely to be altered.

Clinical experience with the 14 valent vaccine in the United Kingdom is limited at the moment and only time will tell as to its prophylactic value in preventing severe pneumococcal disease, and thus decreasing morbidity and mortality as has been shown in other high risk groups (Riley et al., 1977). It is still not known why some pneumococcal types are more invasive than others, why certain types are more prone to cause infection in infancy and why some adults exhibit a poor antibody response to some antigens. The incidence of different pneumococcal serotype varies with time, geographical areas, the age of the patient and the disease process. There is no known explanation for the changes in the incidence of pneumococcal disease nor for type shifts and for these reasons pneumococcal typing surveillance programmes are necessary on national scales to ensure continued optimal vaccine composition to monitor possible shifts in type distribution which may occur due to vaccine usage.

Penicillin has been the mainstay in the treatment of pneumococcal pneumonia and it is unlikely that a more effective anti-pneumococcal agent can be developed, but the medical literature reports the emergence of occasional strains of pneumococci with increased resistance to penicillin (Leading Article, 1977; Meers & Mathews, 1978; Pabst & Nigrin, 1979). It is with this in mind and the continued morbidity and mortality laid at the feet of the 'captain of the men of death' (Osler, 1909) that renewed interest in vaccines should take place. Certain groups of the population are at risk and patients over the age of 50 years with recurrent respiratory problems and underlying disease such as diabetes should be considered candidates for the vaccine. Others with chronic cardiac or renal insufficiency may benefit and patients with homozygous sickle cell disease or those who have had a splenectomy should be given the vaccine. Epidemiological studies of the current importance of the pneumococcus and the efficacy and safety should be part of a continuing programme.

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References


pneumococcal pneumoniae is attributable to the inability of the membrane proteins from resistant penicillin to bind to the penicillin-binding proteins in the cell membrane. Separation of the membrane proteins from resistant bacteria by sodium dodecyl sulphate slab gel electrophoresis has revealed three distinct penicillin-binding proteins; the degree of binding to these proteins is inversely proportional to the level of resistance. Although there is little cross-resistance conferred by these proteins to other antibiotics, two of the resistant penicillin-binding proteins are unable to bind to cloxacillin. Professor Bryan's group has also examined the concentration of certain metabolites in relation to the degree of aminoglycoside antibiotic resistance in Pseudomonas aeruginosa. If a strain is deficient in cytochrome c and nitrate oxidase, it is resistant to aminoglycoside action. Similarly, if the terminal oxidase of the electron transport system is inadequate, the organism is also resistant to aminoglycoside. It is believed that this system is responsible for energizing the membrane sites that allow aminoglycoside transport into the cell. Thus, impaired coupling of this system as a result of a reduction in cytochrome c, nitrate oxidase or terminal oxidase activity leads to aminoglycoside resistance.

This is similar to the system described by Damper and Epstein from Chicago in their paper on chromosomally-determined resistance to aminoglycoside antibiotics in Escherichia coli. These workers propose that in this organism the proton motive force (pmf) is responsible for the incorporation of aminoglycosides. If the electrical potential difference between the outside of the cell and the negatively-charged cytoplasm is great, the pmf is high and the cationic aminoglycosides can readily enter the cell. When the external pH is lower, the pmf is reduced and thus reduces the entry of aminoglycosides with a concomitant increase in minimum inhibitory concentration (MIC). If the pmf is bypassed, by the addition of NADH or by uncoupling of the electron-transport system, the aminoglycosides are unable to enter the cell and the organisms appear resistant.

Barbour, Mayer and Swanson gave a paper outlining the development of chromosomal resistance to mecillinam in Escherichia coli. In a mucoid variant which had been isolated clinically, the MIC of mecillinam increased over 100-fold. The mechanism of resistance does not result from the production of an altered target site, a permeability barrier or drug inactivation and is very specific for this drug. Its exact nature remains unclear.

The study of aminoglycoside resistance encoded by resistance plasmids continues to yield new information. Patzer and colleagues...