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*Streptococcal Infections—A Microbiological Overview***

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FIRST of all, I must thank you for the honour which you have done me in extending your invitation to be your Guest Lecturer on this occasion. The theme of your conference deals with Childhood Infections with special reference to the *Streptococci* and we will now turn to this topic.

Streptococcal infections are common in many parts of the tropics. Reports from Ghana and Nigeria have recorded superficial streptococcal lesions in up to 10% of random samples of villagers and school children,[1] whilst 13% of schoolchildren have been found to be naso-pharyngeal carriers of *beta-haemolytic streptoccocci* in Lagos[2] and also in the West Indies.[3] While the primary infections with these organisms are seldom serious, post-streptococcal sequelae are of major importance, with rheumatic carditis being one of the commonest forms of heart disease in Africa,[4–6] and post-streptococcal glomerulonephritis also being relatively common. *Strep pneumoniae* is a common cause of meningitis in children as well as in adults, and is one of the organisms which may be associated with overwhelming infection in patients with sickle-cell disease or the nephrotic syndrome. Before looking at some of these conditions in more detail, it may be wise to first remind ourselves of the various types of streptococci that are important as human pathogens.

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Classification is primarily based on the changes produced when the organisms, which you will remember, are Gram-positive cocci which tend to grow in chains, are cultured on blood agar medium.

1. *Beta-haemolytic streptococci*: Clear haemolysis round colony.

   Lancefield Groups: Grouping is based on cell wall carbohydrate antigens. Groups A B C D and G are the main human pathogens.
   Group A is divided into more than 50 'Griffith' types on the basis of antigenic differences in two surface protein antigens, 'M' and 'T'.

2. *Alpha-haemolytic*: Ill-defined greening and partial haemolysis round colony.
   (*a*) *Strep pneumoniae*
   (*b*) *Viridans* group

3. *Non-haemolytic*: No change in medium

4. *Anaerobic streptococci*: (Peptostreptococci)

Beta-Haemolytic Streptococci

Lancefield Group A streptococci are responsible for about 90% of human streptococcal infections and the organism has therefore been accorded a specific name, *Strep pyogenes*. Known pathogenicity factors include:

1. The surface M protein, which appears morphologically as fimbriae and inhibits phagocytosis. Antibodies against M protein against further infection by strains of the homologous M type, but not against acquisition of carriage of the organisms.

2. Erythrogenic toxin, formed by certain lysogenic (phage-carrying) strains, and responsible antibodies against the toxin protect against further attacks of scarlet fever, but not against infection even if the infecting strain forms the toxin.

3. Hyaluronidase, Streptokinase and Streptodornase, all of which aid the spread of *Streptococci* through the tissues. Streptolysin 0, although cardiotoxic in experimental animals, plays no apparent part in human disease. It is, however, antigenic and antibodies to Streptolysin 0 are used as marker of recent Group A streptococcal infection (ASO titre). Little is known of the factors responsible for the pathogenicity of the other important groups, B C D and G.

Infections Caused by Beta-Haemolytic Streptococci

1. Groups A C G

These three groups can cause similar types of infection, with Group A being markedly predominant, as already mentioned.

Pharyngeal Infections

Infection acquired by inhalation can result either in disease or in a symptomless carrier state. Clinical illness, if it occurs, develops some 48 hours after infection and consists of sore throat and tonsillitis, sometimes with spread to the middle ear and mastoid sinuses. Scarlet fever develops in non-immune patients if the infecting bacterial strain forms the erythrogenic toxin.

Skin Infections

These are common in the tropics and usually present as infected sores or as impetigo, but occasionally, as the more serious spreading infection of Erysipelas.

Other Infections

Other organs can be involved either initially or as a complication of throat or skin infections, following spread of infection via the lymphatics and bloodstream. These include the meninges, nasal sinuses, pleura and female genital tract (puerperal sepsis), bones and joints[7] and death can sometimes follow rapidly in cases of *Strep pyogenes* septicaemia.

2. Group B.

Group B streptococci had been known to be a cause of bovine mastitis for many years, but in the late 1930's they were recognised as possible human pathogens.[8] Group B *streptococci* are carried in the vagina of about 18% of women of child-bearing age in Nigeria. The organism can be sexually transmitted, and vaginal carriage rates are higher among women attending the Sexually Transmitted Diseases (STD) clinics for other complaints.[9] [10] Adult infections can occur, especially in the respiratory tract and skin,[11] but Group B infection mainly involves infants. Infections in infants are generally classified as:

'Early onset' disease in which septicaemia occurs within 10 days of birth, but usually within the first 36 hours of life. There is a high case fatality rate.[12]

'Late onset' disease in which meningitis occurs about the 3rd week of life. This form of the disease is associated with low case fatality rate.[13]

Infection is acquired during delivery, or occasionally by nosocomial spread in newborn infant nurseries. These infections seem to be important in the USA, but evidence from many tropical countries indicates that despite the high vaginal carriage rates, clinical disease in infants is rare.

The reasons for this difference in the epidemiological pattern of the disease between tropical and non-tropical areas is unknown.

3. Group D.

Group D *streptococci* (enterococci) are normal bowel inhabitants. Their main relevance to childhood infection is that they can cause subacute bacterial endocarditis, which itself may be a sequel to rheumatic carditis.

Sequelae of Lancefield Group A Streptococcal Infections

Rheumatic fever

There is usually a preceding acute infection by *Strep pyogenes* about three weeks before clinical features of rheumatic fever develop. The first attack is usually in the young child and in temperate countries almost always follows a pharyngeal infection, although in the tropics, a preceding skin infection is more common. Rheumatic carditis develops in about 30% of patients, but a fleeting polyarthritis, a common symptom in temperate countries, appears to be rare in the tropics.[14] Very advanced rheumatic heart disease has been reported in children as young as 6 years in many tropical countries of Africa and the Far East.[15] Repeated attacks of rheumatic fever may follow clinical or subclinical infection with any of the Griffith types of *Strep pyogenes;* the likelihood of repeated attacks can be reduced by long-term penicillin prophylaxis.

Although the exact pathogenesis of rheumatic carditis is still uncertain, it is likely that an immunological disease process is involved. It is known for instance, that sera from patients with rheumatic fever and rheumatic carditis contain antibodies which will react with both cardiac muscle cells and an antigen present in *Strep pyogenes.* Antibodies are also formed against *Strep pyogenes* antigens which cross-react with antigens present in the connective tissue of human heart valves and other organs. Similarly, in Sydenham's chorea, a rare manifestation of rheumatic disease, serum antibodies can be detected which cross-react both with the *Strep pyogenes* and with antigens present in the caudate nucleus of the human brain.

Post-streptococcal glomerulonephritis

There is also an association between this condition, which occurs in both tropical and temperate parts of the world[3] [16] and prior infection by certain nephritogenic sero-types of *Strep pyogenes*, especially Types 4, 12, 25 and 49. The condition has also occasionally, followed infection by Group C strains.[17] It is not known what exactly makes a particular strain nephritogenic; not all strains of these serotypes are liable to cause glomerulonephritis and there is no reliable *in vitro* test which will distinguish between nephritogenic serotypes and non-nephritogenic strains of similar serotypes.

Post-streptococcal glomerulonephritis appears to be an immune-complex disease, with antigen-antibody complexes being deposited in the glomeruli, where they activate complement, causing inflammation and cellular damage. Most patients recover completely, but a few develop progressive renal damage, possibly because the damaged cells of the glomerular basement membrane can themselves, activate complement via a 'nephritogenic factor' present in the patient's serum and the alternate pathway of complement activation. There is no clear evidence regarding predisposing genetic factors, although some such mechanism is clearly a possibility. The damaged basement membrane cells can also lead to the production of antibody which cross-reacts with the basement membrane of lung alveoli, to cause a haemorrhagic lung disease known as 'Goodpasture's syndrome'. Recurrent attacks of post-streptococcal glomerulonephritis are rare, possibly because there are rather few 'nephritogenic' types of *Strep pyogenes.*

Alpha-Haemolytic Streptococci

Strep pneumoniae

There are 83 different serotypes of *Strep pneumoniae*, distinguishable by antigenic differences in their capsular polysaccharides. Luckily, only about 25 of them are commonly involved as human pathogens. The capsule is essential for pathogenicity and antibody against the capsular polysaccharide is protective and type-specific. *Strep pneumoniae* is a normal inhabitant of the nasopharynx and a carrier rate of 44% was found among children in Ibadan, whilst the carrier rate among adults was 12%.[18] Infection is spread from person to person by droplets of nasal and nasopharyngeal secretions.

Measles predisposes to pneumococcal infection,[19] but children with sickle cell disease or the nephrotic syndrome are at particular risk,[20] as are patients with Hodgkin's disease and splenectomised patients who fail to form IgM antibody in response to pneumococcal challenge.[21–23]

The two most important *Strep pneumoniae* infections are meningitis and pneumococcal pneumonia, although pneumococcal bacteraemia without any obvious source of infection, is also common,[24 25] but rather than considering these in detail, it will be of more interest to consider the general question of pneumococcal infection in sickle-cell disease and the nephrotic syndrome.

Strep pneumoniae in sickle-cell disease and nephrotic syndrome

Sickle-cell disease implies the presence of two abnormal genes concerned with haemoglobin formation, one of which will determine the production of haemoglobin S. Thus, from the point of view of infection, the term 'Sickle-cell disease' may be taken to include not only sickle-cell anaemia (HbSS), but also such conditions as Haemoglobin C disease (HbSC) and Thalassaemia (HbS-Thal). Sickle-cell disease is common in Africa, the phenotypic gene frequency being variously reported as between 10 and 45%, so that in many parts of the continent, up to 1% of the children born can be expected to develop sickle-cell anaemia.[26] Patients with sickle-cell disease are highly susceptible to infection by capsulated bacteria and infection is the main cause of death among children with this condition.[27] Meningitis and septicaemia due to *Strep pneumoniae* are among the most important infections in children with sickle-cell disease, although other infections including osteomyelitis, urinary tract infections and gastroenteritis, due to *Salmonellae*, *Escherichia coli* and member of the *Klebsiella-enterobacter* group may all prove fatal, as, of course, may meningitis by other capsulated organisms such as *H influenzae* and *N meningitidis*.

It should be noted that not only are children with sickle-cell disease likely to suffer fatal infections by these organisms, but that they are also much more likely to acquire them than are normal children. One study, for example, has shown that children with HbSS disease, particularly those under 5 years of age, are some 600 times more likely to develop pneumococcal meningitis, over 100 times more likely to develop *H influenzae* meningitis, and about 25 times more likely to develop salmonellosis than are normal children living in the same environment.[28]

Children with sickle-cell disease have two major defects in their defence systems, which render them so susceptible to infection by capsulated bacteria. These defects are (*i*) functional asplenia and (*ii*) defect in the alternative pathway of complement activation.

Asplenia

The enlarged spleen that can be detected in most children with sickle-cell disease by the age of six months or so, gradually diminishes in size due to a process known as 'autosplenectomy', following repeated episodes of infarction and fibrosis. Even those children whose spleen is stil clinically enlarged may, however, suffer from a 'functional asplenia', demonstrable by the presence of nuclear fragments (Howell-Jolly bodies)

in their red blood cells and by a decreased clearance of intravenous radioactively labelled colloidal sulphur.[29] This loss of splenic function leads to impaired filtering and phagocytosis of bacteria circulating in the blood stream, as well as a lessened production of specific antibody, IgM, and Tufsin, a tetrapeptide identical with part of the IgM molecule, that is thought to promote phagocytosis.

Defect in alternate pathway of complement activation

The exact nature of the defect is not known, but Factor B levels are generally low, due either to a defect in production or possibly to continual activation of the alternate pathway by the need to clear sickled cells from the circulation.[30] Factor B depletion is not the only defect, however, since in some cases, function of the alternate pathway can be restored *in vitro* by the addition of Factor B depleted, but otherwise normal, serum.

The overall effect of the malfunctioning of the alternate pathway is that there is a lack of C3b, an important opsonizing agent in the absence of specific immune IgM or IgG. This lack of C3b is almost certainly responsible for the increased susceptibility of patients with sickle-cell disease and nephrotic syndrome to overwhelming infection by *Esch coli*, *H influenzae*, and *Salmonellae*, in addition to *Strep pneumoniae*. All of these organisms possess a polysaccharide capsule or cell envelope and are difficult for a phagocytic cell to ingest unless first opsonised.It has, in fact, been demonstrated in experimental animals that depletion of the alternate pathway components leads to a lethal failure in the intravascular clearance of *pneumococci*. Thus, the evidence is very strong that it is a fault in this complex mechanism which is responsible for much of the mortality from severe infection that accounts for the early death of many patients with sickle-cell disease.

Strep pneumoniae in meningitis and the use of vaccines

Strep pneumoniae is a major cause of meningitis among older children and adults in Africa; a recent study in Ibadan has shown it to be responsible for 87% of cases of proven bacterial meningitis among those over 15 years old and 47% of those under that age.[31] Children with sickle-cell disease are more likely to develop pneumococcal meningitis than are normal children, but the actual course of the disease is similar in the two groups.[31] The mortality rate in Africa is around 50%, despite full antibiotic therapy, compared with a 20% mortality rate in the temperate regions of the world. The African patient appears in general, to be unduly susceptible to pneumococcal infection, but apart from the specific cases of sickle-cell disease and nephrotic syndrome, the reason for this increased susceptibility remains unknown. It cannot be linked with any known immunological defect.

Useful protection against pneumococcal infection can be obtained by vaccination. Pneumococcal vaccines were first introduced some 30 or more years ago, but interest in them waned with the advent of the antibiotic era and is only recently re-awakening. As already mentioned, there are some 83 different serotypes of *pneumococci*, 25 of which are responsible for around 90% of human infections. Presently available pneumococcal vaccine contains 14 different highly purified capsular polysaccharides. Antibody response to most of these is good, except in the very young child and in the elderly patient. Attempts are being made to increase the number of components in the vaccines to cover all 25 common pneumococcal pathogens, or alternatively, to formulate two separate vaccines that would cover the complete range of important serotypes. Attempts are also being made to increase the antigenicity of some of the components, by incorporating the protein elements from the outer membrane of the bacterial

cell. Preliminary studies, mainly involving protection from pneumococcal pneumonia, are promising, and it is likely that this type of vaccine will prove to be an important adjunct in the management of normal patients as well as of those with sickle-cell disease. It should be noted however, that data on the efficacy of pneumococcal vaccines in children with sickle-cell disease is not entirely clear-cut. Older children appear to have been vaccinated successfully, but efficacy is probably substantially less in the important under-5-year old age group.

The Viridans group of Streptococci

Strep viridans itself does not exist as a bacterial species, but is a name often given to a group of alpha-haemolytic streptococci. I only wish to draw particular attention to two of these species namely: *Strep sanguis*, which is the commonest cause of subacute bacterial endocarditis and, possibly more importantly for the child, *Strep mutans*, which is the organism which initiates dental caries.[32] Although most of you here today are physicians, I will nonetheless, suggest to you that while you are concentrating on streptococcal disease in childhood, it may well be that the *Streptococcus* that will cause the most trouble to the Nigerian children during the ensuing years will be *Strep mutans* and not one of the other more dramatic pathogens we have already considered. A decade or so ago, most children did not even like sweets, certainly they were not widely eaten. But with the growth of the local sugar industry, there has been a progressive increase in the amount of refined carbohydrate eaten by young children and a proportionate decline in their standard of dental health. A rapid glance into the mouths of children in any of your outpatient departments will, I am sure, disclose a high proportion with one or more decayed teeth. Again, one does not have to be a dental surgeon to know that premature loss of deciduous teeth due to caries can adversely affect the oncoming permanent dentition. *Strep mutans*, by its action in forming highly adherent dextrans from sucrose and its production of large amounts of acid by fermentation of other carbohydrates, is and will be, one of the more important pathogenic bacteria affecting Nigerian children in the future.

Mr Chairman, distinguished Ladies and Gentlemen, may I once again, thank you for inviting me to deliver this address and end by wishing you a most successful conference.

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