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Vaccination against *Haemophilus influenzae* b disease

Should almost eradicate the disease if uptake is high

Haemophilus influenzae is common in the nasopharynx, sometimes causing low grade infections such as otitis media and exacerbations of chronic bronchitis. A few strains possess a polysaccharide capsule which confers greatly increased virulence. Such capsulated strains of *H influenzae* can cause serious, sometimes life threatening, illnesses, of which meningitis is the most common. Epiglottitis, arthritis, cellulitis, pericarditis, and pneumonia are other manifestations, usually accompanied by bacteraemia. While disease due to non-capsulated organisms is seen at any age, nearly all infections due to capsulated strains occur in infants and young children. From this autumn a vaccine will be introduced that promises to reduce dramatically infections caused by the most common strain of capsulated *H influenzae*.

Pittman was the first to recognise capsulation and its association with invasive disease[1]; subsequently she identified six capsular serotypes (a-f). Strains with the type b capsule cause almost all invasive haemophilus disease. In England and Wales the incidence has been rising steadily for many years, with over 1200 cases reported last year. Infection rates peak in the second six months of life and decline rapidly thereafter as natural immunity is acquired.[2] Nevertheless, one child in 600 will have experienced invasive disease caused by *H influenzae* b before reaching the age of 5. Mortality in Britain is about 3-5% in children, but 10% of survivors suffer permanent neurological sequelae, most commonly deafness.

Type b capsular polysaccharide is a polymer of ribosylribitol phosphate, widely known as PRP. Immunity is correlated with the presence of antibody against the capsule, and prevention of *H influenzae* b disease by vaccination with PRP has long seemed an attractive proposition. Unfortunately, polysaccharide antigens do not stimulate memory T lymphocytes, so, although they provoke an immune response, protection can be shortlived. Furthermore, they are only weakly immunogenic in young children, the group at greatest risk of infection with *H influenzae* b. Conjugating PRP to an immunogenic "carrier" protein overcomes both these problems. Diphtheria and tetanus toxoids and a meningococcal outer membrane protein have all been used. These conjugate molecules are capable of priming memory T cells, giving long lasting immunity, and of evoking a satisfactory immune response to *H influenzae* b even in young infants.

There is now a wealth of experience with conjugated *H influenzae* b vaccines resulting from their use in Finland, the United States, and Canada. With a single exception,[3] large studies of efficacy have consistently shown better than 90% protection in infants and children who have received at least two doses of vaccine.[4-6] In Finland last year there were only 12 cases of disease caused by *H influenzae* b compared with 150-200 cases annually in previous years. Conjugate *H influenzae* b vaccines are safe; side effects are rare and usually limited to local redness or a mild febrile reaction.[7,8] Worldwide, many millions of doses have now been given without any permanent adverse effect.

Recent studies in Oxford and Gloucester confirm that these vaccines are immunogenic when given to infants at 2, 3, and 4 months. *H influenzae* b vaccine is now being introduced into the Oxford regional immunisation programme and will form part of the national childhood immunisation schedule from this October. All children born after July this year should receive three doses of the vaccine intramuscularly at monthly intervals starting at 2 months—for example at the same time as they receive diphtheria, tetanus, and pertussis vaccine. For the moment the two vaccines should be given at different sites. Later, when trials of combined preparations have been completed, quadrivalent diphtheria, tetanus, pertussis, and *H influenzae* b vaccines should become available. A catch up exercise will be needed to protect children aged 2-48 months when the vaccine is introduced. Children under 13 months will require three doses of vaccine whereas those aged 13-48 months need only one. When convenient, *H influenzae* b vaccine can be given at the same time as measles, mumps, and rubella vaccine, though in a different limb. Child health computers will schedule appointments for all children in the target age group, starting with those aged less than 13 months. No one older than 48 months needs the vaccine.

The objective of the campaign is to complete the immunisation of all target children by October next year. The impact on *H influenzae* b disease will be almost immediate, because most infections occur in the very young. If uptake of the vaccine is high *H influenzae* b disease could be virtually eliminated from Britain within two to three years. The vaccine will not prevent other types of bacterial or viral meningitis, nor will it reduce the risk of disease due to non-capsulated *H influenzae*.

The new *H influenzae* b vaccines represent an important advance in the chemical manipulation of bacterial antigens to improve their immunogenicity. Applying similar technology to the capsular polysaccharides of other invasive bacteria such

as meningococci holds exciting promise for the future. More immediately, we may look forward with confidence to a rapid and dramatic reduction of *H influenzae* b disease in Britain.

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Managing the persistent vegetative state

Early, skilled treatment offers the best hope for optimal recovery

The persistent vegetative state is one of the least understood conditions in rehabilitation medicine. Originally coined by Jennett and Plum, the term describes the behavioural features of profoundly brain damaged people who, though having a sleep-awake pattern, respond on a reflex level without evidence of cognitive functioning.[1]

The term is unfortunate. Many people understand "persistent" to mean "permanent"—that is, a statement of final outcome rather than a comment on the present state. "Vegetative" has the unfortunate connotation of "vegetable-like." Neither of these interpretations encourages a positive approach to treatment.

Knowing when persistent becomes permanent is difficult. Berrol found that when the persistent vegetative state lasted less than six months one third of patients had moderate levels of disability; when it lasted longer than six months all remained severely disabled.[2] In a study of 84 patients who were in a persistent vegetative state 34 became aware by six months, a further 10 by one year, and a further 5 by three years.[3] There have also been several reports of recovery taking place after up to five years in a persistent vegetative state. These all confuse the picture as to what should be done and when.

Early on in management most attention is directed towards diagnosis and lifesaving measures, and this stage is usually carried out with great skill. Unfortunately, as Jennett pointed out, "in some hospitals, there seems not much middle ground left between intensive care and relative neglect."[4] This is probably unsurprising as each health authority will have only two or three people in a permanent vegetative state. Rehabilitation units are often unable to accept these patients as a priority, and therefore they remain on general medical, surgical, or orthopaedic wards, where there is little opportunity to develop the skills to manage them. At present, Britain has only one dedicated unit for rehabilitating and managing people with this condition.

What can be achieved? General management is based on good standards of nursing care—preventing pressure sores, controlling bowel and bladder function, managing the tracheostomy, controlling infections, and avoiding contractures. Clinical observation suggests that sitting the patient in a chair results in increased eye opening, and many patients benefit from specialist seating systems to maintain the control of muscle tone.

Nutrition is often neglected. Brain damaged patients admitted for rehabilitation are on average 85% of their ideal weight.[5] This is unsurprising as maintaining nutrition through a nasogastric tube may take up to three hours of nursing time a day. Endoscopically placed percutaneous gastrostomy tubes are an important advance in managing nutrition for such severely disabled people.[6]

The role of drugs in the management of the persistent vegetative state is still uncertain. Many patients receive antiepileptic drugs; those with a lower cerebral inhibiting effect, such as carbamazepine, should be considered. Clinical observation suggests that bromocriptine may improve levels of awareness, though this has yet to be formally assessed.

Coma arousal programmes are attracting interest. These use stimulation of vision, hearing, touch, taste, and smell, starting at a simple level and then building up to more complex stimuli as the conscious level improves. There is still much to learn—for example, whether familiar sounds are more effective than noise or unfamiliar sounds. Similarly, with the duration of stimulation: at the Royal Hospital it is our impression that short bursts of less than a minute, repeated intermittently with periods of silence over quarter of an hour, are all that patients in a persistent vegetative state can tolerate. Because of this the unit schedules quiet periods for the whole ward several times a day.

Some evidence is emerging that stimulation programmes can affect responses. Wilson *et al* found that a multimodal stimulation programme significantly benefited four patients, though a unimodal programme did not.[7] Other researchers have found changes in the ratio of θ to β activity in the electroencephalogram of half the patients entered into multimodal stimulation programmes[8]; Sisson found electroencephalographic changes and eye opening responses to a stimulation programme.[9] Although these effects are encouraging, they are unlikely to make a clinical difference.[10]

Of more clinical relevance is 10 years' experience of training relatives of more than 250 patients in a persistent vegetative state to use a programme of stimulation every quarter of an hour for up to 11 hours a day.[10] In this study only 4% of patients did not improve; one third became functionally independent. In a randomised controlled trial a stimulated group had a shorter duration of coma, which lightened more rapidly, than that in the control group.[11] Methodological difficulties exist with all of these studies—because of the small number of affected patients available for study there is a tendency to bring together, for purposes of statistical testing, groups who ought to be kept distinct.[12] New arousal programmes of deep brain stimulation are being developed,[13,14] which may offer further options for treatment in the relatively near future, though these need full evaluation.