The continuing problem of pneumococcal infection

Since the introduction of the sulphonamides and then penicillin 40 years ago, there has been little improvement in the therapy of pneumococcal bacteraemias. Two recent reviews (Burman, Norrby & Trollfers, 1985; Gransden, Eykyn & Phillips, 1985), from Stockholm and London, reported an overall mortality for pneumococcal infections of 20% and 28% respectively. There is a higher mortality at the extremes of life and in patients with underlying disease (particularly alcoholism or chronic lung disease) or immunological abnormality. The Stockholm study found a mortality of only two per cent for those aged between 18 and 65. Many patients dying of pneumococcal bacteraemia were moribund on admission or died within 48 h of beginning appropriate antibiotic therapy. Although the pneumococcus may still be considered 'the old man's friend' (Gruer, McKendrick & Geddes, 1984), there must be many cases of pneumococcal infection in the elderly where we should consider means of reducing the mortality.

Penicillin, and many other β-lactam antibiotics, are highly active in vitro against Streptococcus pneumoniae. There are few direct studies comparing the efficacy of penicillin with other antibiotics for severe pneumococcal infections. There have been many studies comparing different β-lactams in chest infections, a proportion of which have been due to S. pneumoniae (e.g. Rodriguez et al., 1982; Garcia-Rodriguez & Gomez-Garcia, 1984; Bitner et al., 1986). It would be interesting to see whether the higher serum levels attainable with third generation cephalosporins compared with penicillin would produce better results in pneumococcal septicaemia. Other groups of antibiotics could also be compared with penicillin: the quinolones in general have only modest in-vitro activity against S. pneumoniae (King, Shannon & Phillips, 1984) but results of in-vivo studies suggest that ciprofloxacin, in particular, may merit further assessment in pneumococcal infections (Gleadhill, Ferguson & Lowry, 1986).

The existence of pneumococci with intermediate resistance to penicillins, with typical MICs of 0.1–1.0 mg/l for penicillin, was recognized in the 1940s. Since 1978 penicillin resistant pneumococci with MICs of 2–10 mg/l for penicillin have been seen. Pneumococci with individual resistance to tetracycline, erythromycin, chloramphenicol, clindamycin and rifampicin have also been reported, with some isolates resistant to all the above antibiotics (Jacobs et al., 1978; Ward, 1981; Tweeddy, Jacobs & Speck, 1983). Pneumococci with intermediate or full resistance to penicillin have usually been reported as sporadic isolates, commonly from children (Ward, 1981) although experience from South Africa shows that the organism can spread in a hospital. In one of our hospitals 20% of all pneumococcal infections were hospital acquired, although there was little evidence that the pneumococci were acquired from primary cases (Davies & Lockley, 1987). A prevalence study of pneumococci colonizing Spanish children (Pérez et al., 1987) found that over one third of 159 pneumococci isolated showed intermediate or full resistance to penicillin. Results like this would make it not practical to attempt to eradicate carriage of such resistant strains among contacts of the index strain. In countries where resistant pneumococci are less commonly encountered it might be feasible to identify and treat carriers of resistant pneumococci although there have been few published reports on this. Rifampicin (perhaps combined with trimethoprim) should be considered for use here, although there may be a danger of producing rifampicin-resistant pneumococci. We feel that, unless there is evidence of cross infection with pneumococci with moderate or full resistance to penicillin, there is currently no indication to screen or treat potential carriers, although all significant isolates of pneumococci should have discriminating primary sensitivity testing, with determination of MICs of some antibiotics when indicated.

It is unclear why pneumococcal infections have such a high early mortality. In 1964, Austrian & Gold said that 'antibiotic therapy has not reduced the mortality in the first days of therapy of bacteraemic pneumococcal
infections', and, even with the availability of intensive care facilities, that view still holds today (Austrian, 1984).

The key components of host defence against pneumococcal sepsis are antibody, complement, neutrophils and an intact spleen. Since antibodies are the only component which can be enhanced, recent research aimed at reducing morbidity due to this organism has concentrated on the use of pneumococcal vaccines. The possession of a capsule is essential for the virulence of \textit{S. pneumoniae} (Rich & McKee, 1939). Clinical and experimental data gathered over the last 100 years have established the protective value of type specific anti-capsular antibodies (Fraenkel, 1886; Austrian, 1984). Transplacentally acquired antibodies confer on infants a measure of protection against pneumococcal infection, which disappears by six months of age. Effective antibody responses to polysaccharide antigens do not appear till two years of age (Granoff, 1980); maturation of some anti-polysaccharide antibody responses may be delayed up to 8 years of age (Schur, Rosen & Norman, 1979; Buckley, Dees & O'Fallon, 1968). Healthy adults respond to pneumococcal capsular polysaccharide vaccine which behaves as thymus independent antigens (Mosier & Subbarao, 1982) and induces specific antibodies of the IgM, IgA, IgG1 and IgG2 isotypes (Oldfield et al., 1985).

The relative in-vivo protective efficacy of anti-capsular antibodies of each heavy chain isotype has not been clearly established. However, circumstantial clinical evidence supports the pre-eminence of the IgG2 subclass in this context. Patients who are selectively deficient in IgA and IgG2 appear to be especially prone to recurrent respiratory infections, while IgA deficient individuals who are asymptomatic have normal serum IgG2 levels (Oxelius et al., 1981; Hammarström et al., 1984). Furthermore a subset of IgA deficient patients, with normal serum IgG2 levels but a deficient IgG2 response to pneumococcal polysaccharides, appear to be highly susceptible to pneumococcal sepsis (Lane & MacLennan, 1986).

A revised 23-valent anti-pneumococcal vaccine has been recommended for certain high risk groups (American Academy of Pediatrics, 1985) including those with sickle cell disease, nephrotic syndrome, and new cases of Hodgkin's disease before institution of anti-neoplastic therapy. Splenectomy significantly increases the risk of fulminant pneumococcal sepsis, primarily owing to the loss of the filtering capacity of its red pulp macrophages (Hosea et al., 1981). Although it is prudent to vaccinate before elective splenectomy or after emergency splenectomy, boosting antibody responses alone may not compensate for the loss of this major phagocytic reservoir. As vaccination failures may occur in splenectomized individuals (Oldfield et al., 1985) and pneumococcal sepsis due to primary or secondary antibody deficiency (Thompson & Rees-Jones, 1976; Buckley, 1985). Replacement therapy may also be appropriate for bone marrow transplant recipients, as anti-polysaccharide responses are slow to recover after this procedure (Meyers & Atkinson, 1983; Witherspoon, Lum & Storb, 1984).

Two at-risk groups that are unlikely to benefit from the current pneumococcal vaccine are children below two years of age and the elderly. Simberkoff et al. (1986) have documented that elderly individuals may have deficient antibody responses to pneumococcal polysaccharide vaccines. Can the immunogenicity of pneumococcal vaccines be enhanced in these two groups? Children respond to 'thymus-dependent' protein antigens such as tetanus toxoid from an early age. Conjugation of capsular polysaccharides to protein carriers such as tetanus toxoid overcomes the physiological inability of young children to produce antibodies directed against the polysaccharide moiety, as has been demonstrated for \textit{Haemophilus influenzae} type b (Hib) capsular polysaccharide (Eskola et al., 1985; Lepow et al., 1986). Even selectively IgG2 deficient patients appear to respond to Hib polyribosylribitol phosphate-tetanus toxoid conjugates with the production of specific antibodies of the IgM and IgG isotypes which have bactericidal activity in vitro. While the initial promise of this approach needs to be substantiated by demonstration of clinical efficiency of conjugate vaccines, these results point the way towards second generation pneumococcal vaccines. These are likely to be more difficult to produce than conjugate Hib vaccines owing to the multiplicity of pneumococcal serotypes.
involved.

What else can be done to reduce the mortality of severe pneumococcal infection? In animal models of pneumococcal infection, eradication of pneumococci did not prevent death (Perry & Cluff, 1966). Furthermore, Dick & Gemmell (1971) showed that antibiotic therapy is ineffective after a certain point in pneumococcal infection. A study of the pathogenesis of meningococcal infection by pneumococci showed that both major cell wall components, teichoic acid and peptidoglycan, were active in causing inflammation, whereas capsular polysaccharide and degraded teichoic acid had little activity (Tuomanen et al., 1985). Hence the cell wall, or fractions of the cell wall, appear to be the key components responsible for the harmful effects of pneumococcal infection. It has been suggested that mortality in pneumococcal pneumonia may be due to activation of the alternative complement pathway by the pneumococcal cell wall (Reed et al., 1984), leading to shock in a manner not dissimilar to endotoxaemia, although the pneumococcus is a Gram-positive organism. The current pneumococcal vaccine is directed against capsular polysaccharides which help protect the pneumococcus against phagocytosis. It would be interesting to see if a vaccine developed against the cell wall components active in the pathogenesis of pneumococcal infection would be effective in reducing the morbidity associated with this illness.

If components of the pneumococcal cell wall are capable of causing death, improving antibiotic regimens alone may not significantly reduce mortality. Passive immunotherapy with type-specific antiserum was widely used until the introduction of sulphonamides (Finland & Brown, 1939; Finland, 1942). This therapy produced some promising results, although there was a suspicion that the combination of sulphonamide and rabbit type specific antipneumococcal serum resulted in a higher mortality than the administration of sulphonamide alone. This was probably caused, however, by the administration of serum to severely ill patients who had responded slowly to the initial sulphonamide therapy. Specific immunotherapy may be given too late in the course of an infection to be optimally effective unless rapid methods of detecting the specific serotype responsible for pneumococcal infections in individual patients are routinely available.

Some commercial immunoglobulin preparations have a high titre of anti capsular antibody directed against the common pathogenic pneumococcal serotypes (Von Muralt & Sidiropoulos, 1981). It would be interesting to see if the addition of serotherapy to antibiotic regimens is of benefit in pneumococcal infections, as has been shown for gram-negative endotoxaemia (Ziegler et al., 1982). Alternative therapy such as plasmapheresis or exchange transfusion may help to reduce endotoxaemia, as with meningococcal infections (Bjorvatn et al., 1984). The persistent high mortality of severe pneumococcal infection in the post-penicillin era should be a spur for research into optimal therapy for this condition.

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**The treatment of viral warts with interferons**

Viral warts are benign tumours caused by infection of the epithelium of susceptible individuals with a member of the human papilloma virus (HPV) group (Bunney, 1982). A large and ever increasing number of viral serotypes has been identified (Weck, Brandsma & Whisnant, 1986) and there is evidence to support a correlation between certain serotypes and specific morphological and histological patterns of disease (Lever & Schaumburg-Lever, 1983; Jablonska *et al.*, 1985). Lesions may be single or multiple and the majority resolve within a year, either spontaneously or following the use of simple local therapies. Susceptibility to persistent, severe or multiple spreading lesions is probably due to a failure of cell-mediated immunity (Jablonska *et al.*, 1985; Bunney, 1986).

Commonly used wart treatments include: the local application of preparations containing salicylic acid with or without lactic acid, glutaraldehyde, podophyllin and formamide; cryotherapy with liquid nitrogen; curettage, electrocautery or electrodessication or a combination of these (Bunney, 1982). However, warts which fail to be eradicated by such treatments and which present a long-standing socially or physically distressing problem for patients are not uncommon in dermatological and genito-urinary outpatient departments.

They represent a frustrating therapeutic experience for patients and doctors and increasingly consume the precious resources of time and money. The lack of successful new therapies which may be used in an unrestricted manner is striking, although a number of experimental modalities, often of limited scope, have emerged in the past two to three decades. These include immunotherapy, photodynamic inactivation, photochemotherapy, topical application of 5-fluorouracil and idoxuridine, and intralesional injections of bleomycin (Bunney, 1982; Bunney *et al.*, 1984). Recently, attention has been increasingly focused on the interferons which possess antiviral, antiproliferative and immunomodulatory properties (Berman & Frankfort, 1982; Burke, 1985) and thus appear to represent a rational choice as a therapy for severe, persistent warts which prove resistant to the rigorous application of conventional treatments. However, it is clear that interferons have the potential to produce a wide range of side effects and adverse reactions following systemic absorption and, as viral warts usually represent a benign, at times extremely troublesome, disease process, it is of importance to achieve the most favourable therapeutic ratio for this form of treatment.

In trying to give an overview of the treatment of warts with interferons, it is important to bear in mind the difficulties imposed by disease heterogeneity both within and between published studies in terms of morphological and histological features and HPV serotype and of duration and severity of disease. In addition, the type of interferon used and the treatment regimen employed need to be considered. It is probable that the immune status of the patient may influence treatment outcome and there is also evidence to suggest a link between the immune status and the presence of certain HPV serotypes (Jablonska *et al.*, 1985). Additionally, a recent study indicates that the duration of disease, at least in the case of condylomata acuminata, may affect response to therapy with interferons (Eron *et al.*, 1986). The greatest effort has gone into investigating the use of interferons in the treatment of anogenital HPV disease. This concentration is probably due to the general perception that warts in anogenital sites provide the patient with a greater burden than those in other locations. This emphasis on anogenital disease has developed further following the suggestion that two of the causative serotypes in this anatomical region (HPV 16 and 18) have...
oological potential (Bunney, 1986). It should not be ignored, however, that severe, non-anogenital cutaneous viral warts may impose significant social and physical limitations on a patient's activities, including threats to livelihood, and that a considerable risk of development of squamous cell carcinoma exists in some patients with the rare HPV-associated disease epidermodysplasia verruciformis.

Sufficient published data currently exist to indicate that various interferons including human leukocyte interferon, human lymphoblastoid interferon-α, recombinant α2-interferons and β-interferon possess the potential to benefit patients with HPV-induced disease (Niimura, 1983; Eron et al., 1986; Gibson, 1986; Weck et al., 1986). Depending on the condition being treated and the preference of the investigator, the intramuscular, subcutaneous, intradermal and topical routes have been chosen. The key question which currently needs to be addressed is: 'What is the optimal treatment regimen for each type of interferon in the major subtypes of HPV disease?' Thus, the ideal route, the dose, the frequency of administration and the duration of therapy producing maximal benefit all remain to be fully clarified. Evaluation of these issues is complicated by the unpredictable nature of HPV disease, including the role of the host's immunological status in disease resolution and the fact that responses to therapy may occur or continue to develop after cessation of treatment.

It does appear that the potential for serious toxicity which interferons undoubtedly possess following systemic absorption can generally be avoided at the relatively low doses needed to provide benefit in the treatment of viral warts. However, it should not be ignored that adverse effects of a less serious nature are common, and sometimes troublesome. These include self-limiting influenza-like symptoms which usually clear within 24 h of treatment. Patients should be carefully assessed when being considered for treatment and interferons should be reserved for motivated individuals with long-standing disease, severe enough to impose significant social or physical limitations on their activities and in whom rigorous application of conventional therapies has failed. The possible adverse effects of interferons, even when systemic availability is unlikely to be low, should be considered in relationship to the presence of other disease processes, the taking of concomitant medications and the age and general robustness of the patient under consideration. Routine haematology, clinical chemistry and urinalysis should be performed before, during and after a course of treatment, in order to detect promptly disturbances, such as a significant drop in the white blood count and elevation of hepatic enzymes which may necessitate a reduction of dosage or cessation of treatment, and to increase the data base concerning the safety of interferons in the treatment of HPV disease.

My personal experience lies in the treatment of severe persistent cutaneous non-genital viral warts with human lymphoblastoid interferon-α (Wellferon), using several different treatment regimens administered by the intramuscular, intradermal and dermstrument routes (Gibson & Harvey, 1984; Gibson et al., 1986; Gibson, unpublished data). The results of treatment of the first 55 patients suggest that the intradermal route of administration is the most advantageous. This is because such therapy provides an impressive rate of complete clearance of the injected lesion (in 21 of 27 subjects), and in cases of multiple widespread disease also appears to provide significant improvement (≥50%) in distant non-injected lesions (in 14 of 18 subjects). Such benefit in distant non-injected lesions may be due to a direct effect of the systemically available interferon, stimulation of the patient's own immunity or a combination of these factors. Successes have been achieved in common, plantar mosaic and deep hyperkeratotic palmo-plantar warts. I currently use a single weekly injection of human lymphoblastoid interferon-α into the 'root' of the largest or most troublesome wart for a period of 12 weeks, although fortnightly injections have also yielded encouraging results. Patients are subsequently followed up for a further 12 weeks as major responses to treatment sometimes occur during this time. The standard dose is 0.3 ml of a 10 mega units/ml concentration but this may be increased to a maximum of 5 mega units per injection or reduced to a minimum of 1 mega unit per injection depending on the patient's response to therapy, including adverse effects. Serious adverse events and clinically significant disturbances of haematological, clinical chemistry and urinalysis parameters have not been observed to date with this regimen of treatment. However, virtually all patients experience self-limiting, transient influenza-like symptoms, sometimes of a severe degree, which may be partially controlled by paracetamol 1 g every 4–6 h. Intradermal injections are undoubtedly associated with pain, prob-
ably due to a fluid volume effect, which varies in degree, depending on the site involved. However, its transient nature, the lack of clinically detectable local tissue damage and scar-free healing of the lesions permits a reasonable level of patient acceptability. While the im route of administration is rapid and convenient, it gives a poor therapeutic ratio; and although dermoejet administration has a reasonable therapeutic ratio it is wasteful of the drug.

Published reports of the treatment of non-genital cutaneous viral warts with interferons are sparse and have yielded variable results. Niimura (1983) demonstrated a statistically significant benefit using intralesional human fibroblast interferon versus placebo in the treatment of common warts, with 81% of lesions in the active treatment group being cleared or significantly improved compared with 17% in the placebo group. Conversely, Vance et al. (1986) failed to demonstrate a statistically significant therapeutic effect for intralesional human recombinant alpha-2 interferon versus placebo in the treatment of verruca plantaris. Direct comparisons between these data and our own results are inappropriate, but it may be worth noting that intralesional injections of interferon vehicle or saline generally yield complete clearance rates of 21% or less (Bunney et al., 1986; Vance et al., 1986).

In summary, it would appear that several different interferons have the potential to benefit patients with HPV disease, and regimens of treatment which provide a reasonable therapeutic ratio for carefully selected patients already exist, but do need fuller evaluation, and can be further refined. However, it is unlikely that any method of interferon usage which permits systemic availability will be appropriate for use in the treatment of anything but severe, recalcitrant HPV disease. It should be noted that no interferon has, as yet, been licensed for this indication and thus use of this agent remains an experimental stage at this time.

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