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Prevention and Treatment of Sepsis in Burns

In the past decade there has been great progress in the understanding and control of burn sepsis. This followed a rather abrupt awakening or re-awakening to its importance as a cause of illness and death after severe burns. In the 1940s and early 1950s *Streptococcus pyogenes* was generally seen to be the most important pathogen; it commonly infected burns, causing failure of skin grafts and sometimes invasive infection. Antibiotic therapy and prophylaxis proved highly effective, and since resistant variants hardly ever emerged, streptococcal infection became a minor and infrequent complication. Staphylococci, Gram-negative bacilli and other bacteria were often found in burns, usually without causing obvious illness or graft failure, and their presence was widely ignored. Those who studied burn infection, however, recognized the pathogenic potentialities of some of these bacteria in some patients. One species in particular, *Pseudomonas aeruginosa (pyocyanea)*, often caused severe invasive infection of tissues, vessel walls and sometimes of the bloodstream in the most extensively burnt patients; the same organism was known for its peculiar aggressiveness towards patients suffering from hypogammaglobulinæmia, leukæmia and other conditions in which the patient had poor resistance. Invasive infection with *Ps. aeruginosa* was found to be associated with some characteristic features – focal hæmorrhagic necroses in skin and viscera, sometimes leading to ecthymatous ulceration, and in some cases leukopenia, hypothermia and paralytic ileus. Skin grafts on infected areas sometimes failed, though less consistently than with *Str. pyogenes*. Other organisms, often present in mixed culture with the pseudomonas, were also apparently involved in the pathogenesis; these included *Proteus* spp., *Klebsiella* spp. and *Staphylococcus aureus*.

Sources of Infection

There has been some controversy about the relative importance of self-infection with *Ps. aeruginosa* carried by the patient in his intestinal flora and of cross-infection from other patients. Our studies showed a low incidence (3–4%) of *Ps. aeruginosa* in the fæces of normal subjects and in patients on admission to hospital; some of the latter did not acquire a pseudomonas in their burns. Phage typing showed that in most cases the strain causing a new infection was of a type that had already been isolated from patients in the same ward, but not in the other ward of the Burns Unit (Davis *et al.* 1969). This strongly supported the view that cross-infection was the main source.

Occasional outbreaks of *Streptococcus pyogenes* infection due to a single serotype and the endemic spread of antibiotic-resistant hospital staphylococci showed that infection also with these organisms was largely acquired in hospital from other patients; in the case of *Str. pyogenes*, however, the outbreak usually started from a patient admitted while carrying or infected with a streptococcus.

Routes of Transfer

About half the nurses on duty in a burns ward with much pseudomonas infection were found to be carrying the organism on their hands. Evidence that hand-transmitted infection was of special importance came recently from a controlled trial in which patients were allocated to groups treated: (1) in a plastic isolator with glove-ports to protect the patient against manual transfer, but with an open top to allow airborne contamination; (2) in an air-curtain isolator, which protected them against airborne but not against contact transfer; and (3) in the open ward, where they had no specific protection against either contact or airborne transfer. It was shown that 5 of 10 patients in the air-curtain isolator and 5 of 10 patients in the open ward became infected with *Ps. aeruginosa;* of those treated in the open-topped plastic isolator, none (out of 10) became infected with the organism. In another trial there was a significant protective effect of plastic ventilated isolators, whether or not filters were present in the air supply to the isolators. From these results we inferred that *Ps. aeruginosa* is transferred in the ward by contact but not by air. An exception to the rule was, however, shown some years ago in a controlled trial of a plenum ventilated dressing room, in which patients acquired significantly less pseudomonas infection than they did when dressings were changed in the same room by the same staff, but with no mechanical ventilation. Staphylococci, as one might expect, appear to be transferred both by air and by contact, and coliform bacilli are apparently often acquired from patients' intestinal flora.

Prophylaxis

Patients can be protected against infection by methods that prevent contamination of burns (the first line of defence) and by methods that prevent invasion of tissues and bloodstream from an already colonized burn (the second line of defence) (Lowbury 1967).

In 1951 we reported that topical application of polymyxin gave significant protection against *Ps. aeruginosa* (Jackson *et al.* 1951). The most promising advance in topical chemoprophylaxis, however, came in 1965 with Moyer's reintroduction of silver nitrate (Moyer *et al.* 1965). In the following year a controlled trial, in our unit, of treatment for severely burnt patients with compresses of 0·5% silver nitrate solution showed striking prophylaxis against *Ps. aeruginosa* and *Proteus* spp.; in addition to the exclusion of *Ps. aeruginosa* from most burns, this led to a significant reduction in mean morning and evening temperature and respiration rate (Cason *et al.* 1966). Since the introduction of such treatment for many severe burns there has been a large fall in the incidence of *Ps. aeruginosa* septicæmia, an overall reduction in the bacterial colonization of burns (Fig 1), and a significant reduction in mortality.

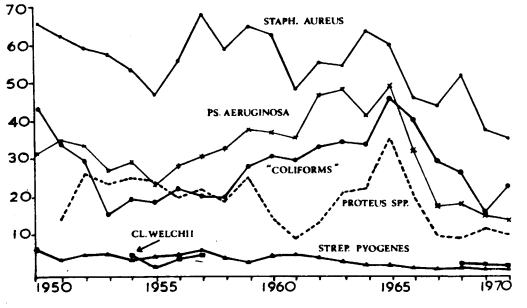

Fig 1 *Bacteria in burns*

We have studied many other forms of topical chemoprophylaxis, including creams containing mafenide (Sulfamylon: p-aminomethylbenzene sulfonamide), silver sulphadiazine, gentamicin, silver nitrate alone and with additives (chlorhexidine, gentamicin); all of these gave protection, but some (e.g. gentamicin, trimethoprim) were unsuitable for prophylaxis because of the emergence of resistant variants during treatment, and others (e.g. Sulfamylon) were often unsuitable because of toxic or irritant properties. One trial showed that daily applications of a bacteriostatic cream gave significantly better prophylaxis than less frequent applications (Lowbury & Jackson 1970). No single method could be picked out as better in every respect than others; for example, silver nitrate compresses were inadequate in removing *Ps. aeruginosa* which had already started to grow in burns, and had little prophylactic value against *Klebsiella* spp. and some other Gram-negative bacilli. For these reasons, alternative methods of prophylaxis have been studied, e.g. the use of isolators, which have already been referred to. *Ps. aeruginosa* was the only organism adequately excluded by this method, which had the disadvantages of being cumbersome and causing difficulty in nursing.

The methods mentioned have all involved protection of the patient against contamination. Another approach is to use the second line of defence – against invasion of tissues and bloodstream. Systemic antibiotics have not been found useful in keeping out Gram-negative bacillary infections, but there have been important advances in immunological control. Our own studies have shown the value of active and passive immunization against *Ps. aeruginosa* in burned mice. One of the most interesting findings (Jones 1971) has been a very early protection of burnt mice within 24–48 hours of giving the first dose of a pseudomonas vaccine prepared by Dr Roderick Jones. This makes the prospect of active immunization for a burnt patient, starting at the time of injury, more realistic than we had thought possible. Parallel studies by Dr Wesley Alexander and his colleagues in Cincinnati have already given promise of useful prophylaxis by vaccines in burnt patients (Alexander *et al.* 1969).

Chemotherapy

Successful treatment for *Str. pyogenes* infections with systemic erythromycin, cloxacillin or methicillin was demonstrated years ago in several controlled trials. *Staph. aureus* was shown, in similar controlled trials, to be removed from many burns by systemic treatment with methicillin, cloxacillin or fusidic acid. By contrast, it has been very difficult to remove *Ps. aeruginosa* from burns. Topical treatment with polymyxin and, more recently, with gentamicin, mafenide and silver sulphadiazine has been shown in controlled trials to remove *Ps. aeruginosa* from some burns, and there is evidence that invasion by the organism can sometimes be averted or arrested with large doses of polymyxin or carbenicillin, or with gentamicin. Where successful elimination of *Ps. aeruginosa* from severely burnt patients has been achieved by systemic therapy, the organism has sometimes already caused irreparable damage by the time the infection was recognized and treatment initiated (Jones

et al. 1966). Carbenicillin resistance, which had not been found in our Unit during the first three years of using the antibiotic, suddenly appeared in 1969, and was shown to be due to a resistance factor apparently transferred, by conjugation, from another Gram-negative bacillus – probably a klebsiella or proteus (Lowbury *et al.* 1969, Roe *et al.* 1971).

Comments

Apart from treatment directed against *Str. pyogenes*, the main advances in the control of infection of burns have been prophylactic. It is fortunate that silver nitrate, an antiseptic with no role in chemotherapy, has been so effective in keeping burns free from the organisms that have caused the most dangerous infections. But a few strains of *Ps. aeruginosa* relatively resistant to silver compounds have been found in the United States, and their emergence in other countries must be anticipated. For this reason alternative methods of controlling infection must be assessed. More attention should, perhaps, be given to the second line of defence, including not only immunological methods but also nonspecific resistance to invasion. The low mortality reported from the burns unit in Stockholm (Birke *et al.* 1964), where no topical chemoprophylaxis is used, suggests that supportive measures used there may be effective in preventing invasion by bacteria which are shown to be colonizing the burns. A comparative trial of silver nitrate compresses and exposure treatment with warm dry air (the Stockholm method) on severely burnt patients is at present being made in Birmingham.

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Current Trends in Research on Burns

The Local Lesion

There is now a good body of knowledge on the threshold conditions for the production of burns. We can also give similar information for burns from microwave, laser or ultrasonic energy sources as well as from the more usual forms of thermal conduction or radiation (Carney *et al.* 1968, Lawrence 1968, 1969, Carney *et al.* 1972). Rather less, however, is known about the underlying biochemical lesion in burns. My colleagues have shown that, in threshold burns of isolated skin, respiration, uptake of phosphate into cells, uptake of sulphate into intercellular substances and synthesis of collagen are all inhibited by the same temperature conditions. All these criteria of damage show similar sigmoid dose-response curves to increasing temperatures. A current problem is, therefore, to try to find the common biochemical lesion responsible for these various forms of damage. If this lesion can be identified it might be possible to correct it to some extent so that otherwise irreversible changes may become reversible.

A similar possibility of reversing apparently irreversible changes arises from recent experiments on the effect of grafts upon burns which are just of full thickness. The work on tangential excision mentioned by Dr D Jackson (Jackson 1972) suggested that we might explore similar phenomena in experimental burns. My colleagues have checked that burns in guinea-pigs parallel clinical experience; they find that the bed produced by excision to the level of punctate bleeding will accept grafts, and that such grafting allows quantities of otherwise dead dermis to survive and be incorporated in the healed wound (Groves & Lawrence 1971). Further studies will be needed to establish whether this effect demands a living graft or whether freeze-dried material or even a simple covering agent produces the same effect. Other beneficial effects of grafting also merit investigation: what, for instance, is the mechanism of the suppression of infection by grafts? This has been claimed for both autografts and heterografts. To what extent would an inert substitute give similar effects? Among local effects we may also consider cutaneous pain