

Clinical aspects of epidermolytic toxins of *Staphylococcus aureus*

Alan Lyell

My interest was drawn to staphylococci by the ramifications of toxic epidermal necrolysis (TEN), and through staphylococci to their father, that remarkable but hitherto almost forgotten man, Alexander Ogston, the centenary of whose classical paper *Ueber Abscesse* (Ogston, 1880) we celebrate in this conference.

I described TEN, which I now prefer to call the scalded skin syndrome (SSS), in 1956 on the basis of four patients seen over the preceding seven years—one at Cambridge, two at Edinburgh, and the last here, at Aberdeen (Lyell, 1956). The essence of this acute, sometimes fatal syndrome is that the skin appears to have been scalded, although there has been no thermal burn. Histopathology was of two kinds, and I was uncertain whether they were stages in the same process or two distinct entities. In one there was total epidermal loss, separation having occurred at the dermo-epidermal junction; in the other there had been an intra-epidermal split at the level of the stratum granulosum. Subsequent events have shown that these are distinct entities, and that intra-epidermal splitting results from staphylococcal disease, although I had no inkling at the start that staphylococci had anything to do with the SSS.

The original four patients had been adult, but, starting with the Aberdeen patient described on my behalf by Catto (1959), first a trickle, and then a flood of children with the scalded skin syndrome was described (Potter *et al.*, 1960; Freedberg & Berg, 1964; Holzel & Jacobs, 1966; Tyson *et al.*, 1966; Koblenzer, 1967; Jefferson, 1967; Lowney *et al.*, 1967; Samuels, 1967). From many of these patients *Staphylococcus aureus* could be isolated, most belonging to phage group II. Parker & Williams and others had already shown that phage group II strains were associated with impetigo, pemphigus neonatorum (which is impetigo of the newborn), and the extremely rare Ritter's disease (Williams *et al.*, 1947; Miller, 1950; Barrow, 1955; Parker *et al.*, 1955; Spittlehouse, 1955; Gillespie *et al.*, 1957;

Schmidt *et al.*, 1957; Parker, 1958; Jessen *et al.*, 1959; Howells & Jones, 1961; Parker & Williams, 1961; London & Rosen, 1961; Van Toorn, 1961; Brundin & Laurell, 1963; Rycheck *et al.*, 1963; Dillon & Smith, 1967; Hermann *et al.*, 1967), rather than the familiar pyogenic manifestations that constitute the generally accepted idea of 'proper' staphylococcal disease.

It so happened that in 1968–9 there was an outbreak of staphylococcal impetigo and the staphylococcal SSS in Glasgow (Lyell *et al.*, 1969). Suspecting that a hitherto unrecognized staphylococcal toxin might be responsible for the 'scalding', I went to John Arbuthnott for help. He has described in his paper the discovery and properties of these epidermolytic toxins (ET).

How does knowledge of ET illuminate the clinical situation? There are two types of human reaction to ET: The usual one is *impetigo*, the rare one *scalding*. Pemphigus neonatorum and staphylococcal impetigo represent the former, Ritter's disease and staphylococcal 'TEN' the latter, the different names having arisen in response to differing clinical circumstances. The distinction between impetigo and scalding is clinically arresting and, we believe, biologically important, so that ET-produced disease should be divided clearly into two groups, impetigo and the SSSS. Here it must be noted that Melish & Glasgow, as well as Elias & Fritsch, whose work in this field has been seminal, take the view that both impetigo and scalding should be included in the SSSS, the former being regarded as the localized and the latter as the generalized form (Melish & Glasgow, 1971; Elias *et al.*, 1977). However, the factor common to both reactions is ET rather than scalding, and in our view the alliterative and memorable term SSSS should be reserved for scalding manifestations, that is to say what used to be called Ritter's disease and staphylococcal 'TEN'. If it is desired to refer collectively to the effects of ET an appropriate term would be staphylococcal epidermolytic toxin syndrome.

What is it that determines whether impetigo or the SSSS shall result from infection? The answer is far from clear. First, we must distinguish between the effect of living organisms and the effect of toxin. Living organisms produce impetigo readily, as laboratory workers will testify. On the other hand, toxin injected into human volunteers produces local but poorly circumscribed scalding, not at all like the well demarcated blister of impetigo. Secondly, we must consider the influence of the soil. Whereas the usual human response to organisms is impetigo, the *only* response of baby mice is the SSSS. Perhaps another way of looking at this phenomenon would be to regard mice as insusceptible to impetigo; baby mice develop the SSSS if effective doses of toxin enter the circulation,

whether this is derived from living organisms or from injected toxin. Animal species differ in their response to ET, for example mice are susceptible, rats are not. Monkeys are susceptible to ET (Fritsch, 1975), and perhaps also to impetigo (Landsteiner *et al.*, 1911). With regard to race, it has been stated that black children are less prone to the SSSS than white (Rasmussen, 1975). Thirdly, there is the question of age. Mouse susceptibility decreases with age, an effect attributed to increased renal clearance of toxin in older mice (Fritsch, Elias & Varga, 1976) though there is no evidence that this is a regular mechanism in humans. Human SSSS is exceedingly rare in adults, though it must be remembered that it is rare at any age. Impetigo is much commoner in children than in adults. Perhaps the information required before the age factor can be properly assessed in human SSSS is the ratio of cases of SSSS to impetigo by age. Fourthly, there is the possibility that antitoxin may be concerned. Fritsch (1975) was unable to find experimental evidence for this in mice. Adult examples of the SSSS have often, but not always, been immunologically compromised; the mechanism might well be better growth of organisms with increased toxin production, or accumulation of toxin resulting from metabolic or renal factors, rather than any effect of antitoxin. Fifth, is the possibility that the organisms fluctuate in pathogenicity: the epidemiology of some classical outbreaks of pemphigus neonatorum could be interpreted in this light (Lyell, 1979).

We speculate that impetigo is connected with living organisms plus toxin, and the SSSS with toxin alone. In our first paper (Arbuthnott *et al.*, 1969) we compared SSSS strains with impetigo ones, and found that the former produced more δ -toxin, though whether this will prove to be important is not clear. Fritsch's view, expressed to me, that impetigo results from the production of ET in situ in the skin, and the SSSS from ET reaching the circulation, may well be true as far as it goes, but it fails to explain the sharp demarcation of impetigo lesions. If there were some factor contributed by the organisms, limiting the spread of impetigo lesions, that might go a long way towards clearing up this mystery.

I like to think that Ogston's shade has been watching our proceedings. I hope he is intrigued by what has happened to the staphylococci that he discovered and named, with the help of the professor of Greek (Lyell, 1977). In the story of ET places and events are interwoven. Ogston worked in Prague as a young man, where he met von Rittershain. It was the news of Lister's new technique of antiseptic surgery that brought Ogston to the Glasgow Royal Infirmary to see it in action, a hospital in which Professor Arbuthnott and I have both worked. There is even the coincidence that a key worker in the field of ET is called Glasgow. Ogston put antiseptic

surgery into effect at Aberdeen, and puzzled out eventually why it worked, through his researches on micrococci. It was while I was in Aberdeen that the threads of the SSS were finally drawn together, and the paper written. You will readily appreciate, therefore, that we feel the occasion clothed with an intimate sense of history, and that we value deeply the opportunity of contributing to this conference.

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