

This Week's Citation Classic®

Lyell A. Toxic epidermal necrolysis: an eruption resembling scalding of the skin.
Brit. J. Dermatol. 68:355-61, 1956.
[Royal Infirmary, Aberdeen, Scotland]

Four patients were described, presenting varying degrees of systemic illness, whose skin appeared to have been scalded, although there had been no thermal burn. The title recorded my idea of the pathogenesis: death and loosening (necrosis + lysis) of the epidermis resulting from a toxemia. [The SCI® indicates that this paper has been cited in more than 230 publications, making it the most-cited paper from this journal.]

Smoke Without Fire

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I regret to announce the death of toxic epidermal necrolysis (TEN), whose birth and evolution were described in *Current Contents* in 1988.¹ TEN proved to be both a syndrome and a semantic mine field, not least because its components were themselves part of other syndromes. Looking back from the vantage point of retirement, I sometimes wonder whether describing TEN was not an example of fools rushing in where angels fear to tread; but, if it was, the concept has proved fruitful. I can see a clear way forward, but it is essential that TEN should be buried first.²

Progress depends on naming the diseases that are the heirs of TEN. There are three: (1) *The staphylococcal scalded skin syndrome* (Case 3), effected by staphylococcal epidermolysins, at that time unknown, but now the subject of an expanding literature. It is defined by intraepidermal cleavage, in contrast to the subepidermal cleavage of the others, which are both severe drug (i.e., medication-induced) eruptions. (2) The more familiar of these has been diagnosed variously as TEN or Stevens-Johnson syndrome (erythema multiforme major), but attempts to distinguish one from the other are in vain, as R. Ruiz-Maldonado has shown,³ for they represent the spectrum of a single disease. I favor

calling this *exanthematic necrolysis* (Case 4), to characterize its explosive efflorescence and febrile course. (3) The third disease is a generalized bullous fixed drug eruption, as described by Kirsti Kauppinen,⁴ which is difficult to distinguish from exanthematic necrolysis and is usually confused with it. I favor calling it *fixed drug necrolysis* (Cases 1 and 2). It is usually less severe than exanthematic necrolysis. The important distinctions are that it recurs as many times as the offending drug is encountered, and that, at any one time, all the skin lesions are in the same stage of development. Exanthematic necrolysis seldom recurs, and the eruption develops a polymorphous character, scalding and areas of blotchy erythema being present simultaneously.

It is difficult to persuade dermatologists that fixed drug necrolysis exists. When the truth dawns, there will be a concerted attempt to unravel the mechanism of the fixed drug eruption, which appears to be a hypersensitivity. It should be a fruitful field for research—there are unaffected areas of skin to compare with affected ones, the reaction is reproducible, and there is an experimental model.⁵

The information gained could be compared with what is known of exanthematic necrolysis, which has so far shown little evidence of being a hypersensitivity. It appears likely that its causative medication requires a cofactor—for example, a flu-like illness. This situation is reminiscent of that in Reye's syndrome, which is attributed to giving aspirin to children suffering from flu-like illnesses, in which it has been speculated that there is augmented release of tumor necrosis factor from macrophages under the influence of nonsteroidal anti-inflammatory drugs.⁶

Ars longa, vita brevis—this is my swan song.
Who will take up the torch?

1. Lyell A. Citation Classic. Commentary on *Brit. J. Dermatol.* 68:355-61, 1956. *Current Contents/Clinical Medicine and CC/Life Sciences* 4 January 1988. p. 14.
2. Requiem for toxic epidermal necrolysis. *Brit. J. Dermatol.* 122:837-8, 1990.
3. Ruiz-Maldonado R. Acute disseminated epidermal necrosis types 1, 2, and 3: study of 60 cases. *J. Amer. Acad. Dermatol.* 13:623-35, 1985. (Cited 15 times.)
4. Kauppinen K. Cutaneous reactions to drugs with special reference to severe bullous muco-cutaneous eruptions and sulphonomides. (Whole issue.) *Acta Dermatol-Venerol.* 52 (Supp. 68), 1972. 89 p. (Cited 85 times.)
5. Mason K V. Fixed drug eruption in two dogs caused by diethylcarbazine. *J. Amer. Anim. Hosp. Assn.* 24:301-3, 1988.
6. Larrick J W & Kunkel S L. Is Reye's syndrome caused by augmented release of tumour necrosis factor? *Lancet* 2:132-3, 1986. (Cited 10 times.)