

Lyell's syndrome: histological, immunohistochemical and serological observations

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Observations of Lyell's syndrome in two girls, one 2 and the other 7 years of age, investigated serologically, histologically and by immunofluorescent technique, are reported.

In both cases the disease had been preceded by a prolonged or repeated treatment with acetylsalicylic acid, in the first case in combination with sulphonamides and antibiotics and in the second in combination with mephenytoin.

Immunofluorescent staining revealed immunoglobulins in subepidermal blisters and along the dermal vessels.

Acetylsalicylic acid has been assumed to have been one of the causative factors of the violent progression of toxic epidermal necrolysis, probably by an antigen-antibody reaction. This has been supported by serologic demonstration of antibodies to acetylsalicylic acid in both cases.

On the basis of four clinical observations, Lyell in 1956 described a new entity, toxic epidermal necrolysis, as a disease distinct from other bullous conditions [10]. Although Lyell attributed the disorder to a toxic response to drugs, some authors suggested a possible allergic genesis [3, 5, 9, 14].

Two cases of Lyell's syndrome were reported from this department in 1963 [12]. As at that time we were unable to clarify the pathogenesis, it seemed useful to report two additional cases investigated serologically, histologically and by the immune fluorescent staining technique.

CASE REPORTS

Case No. 1. A female patient 7 years of age had previously had chickenpox, rubella, pneumonia and frequent common colds for which she was repeatedly treated with acetylsalicylic acid and antibiotics. Before the last admission she had contracted influenza and had been treated with acetylsalicylic acid and sulphamethoxydiazine. After she had been discharged, she had again run a temperature and swelling of eyelids and red patches on her face

had appeared. Tetracycline and acetylsalicylic acid were prescribed. On the next day, the eruption spread over the chest, the child developed dyspnoea and a temperature of 41 °C.

She was admitted to the Children's Hospital with a diagnosis of measles, viral infection and drug rash. The whole skin was covered with a livid-red patchy rash with blisters scattered on the face, haemorrhagic crusts on the lips, aphthous stoma-

titis with necrotic shreds in the oral cavity. The heart rate was 160/min. The patient grew restless and delirious. Blood counts were within normal limits except a shift to the left in the differential count. The prostration deteriorated and the sloughing reached a considerable extent, involving the areas beneath the eyes, earlobes, chest, back and perianal region, reminiscent of a bullous burn inflicted by scalding. A positive Nikolsky's sign was conspicuous.

Hydrocortisone, erythromycin, then alidone, calcium, vitamin C, and B complex, infusion of blood plasma, saline and glucose were prescribed, with aprobarbital for sedation. On the next day the condition was unchanged and four days after the appearance of the rash the child died of cardiorespiratory failure.

Necropsy carried out four hours after death revealed a haemorrhagic bronchopneumonia, necrotizing pseudomembranaceous oesophagitis; a fatty liver with abundant vacuolized nuclei of hepatocytes; thickened basal membranes in the renal glomeruli with moderate proliferation of podocytes; perivascular haemorrhages in the interventricular cardiac septum, the gastric mucosa and in the frontal cerebral lobes, basal ganglia and mesencephalon.

Cultures from the bronchi yielded *Staphylococcus aureus* sensitive to erythromycin, streptomycin and kanamycin, as well as *Pneumococcus*.

Histopathologic investigation of the skin. In areas of minor involvement, hydropic degeneration and vacuolization of the basal layer with a loosening of the dermoepidermal junction occurred together with a progressive disintegration of the basal cell layer with irregularly distributed melanin. Clumps of melanin were scattered in the areas of regressive changes in the midpart of the malpighian layer (Fig. 1). The nuclei in this layer were pushed to the periphery due to intracellular vacuolization, in other places the nuclei were pycnotic, karyorrhectic or karyolysed. In more advanced stages the whole epi-

dermis was spongiotic and finally necrotic (Fig. 2). There were numerous subepidermal blisters filled with granulocytes, histiocytes and proteinaceous fluid with admixture of fibrin (Fig. 3).

No significant elevation of acid mucopolysaccharides was found. The adjacent derm showed marked congestion and oedema, perivascular infiltration by mononuclears and histiocytes, and swelling of collagen fibres. Regressive changes of minor degree were noticed in the hair follicles. The necrotic epidermis was shed and in the final stages only wide areas of de-epithelized derm remained.

Immunofluorescent staining [2] revealed serum albumin in the subepidermal blisters (Fig. 4) and at these sites positive fluorescence was obtained with anti-human IgG antibodies. Using antibodies to human IgG, IgA and IgM, a marked positivity was found in the subepidermal blisters and along the dermal vessels including the capillaries (Figs 5 and 6).

Serologic investigations were carried out in post-mortem serum [11, 13]. The results of these tests proving the presence of antibodies to previously administered drugs are listed in Table I.

Case No. 2. In this girl 2 years of age, history revealed a maternal contact with rubella during the first trimester of pregnancy. The girl had microcephalus and a high degree of myopia. When at 2 years of age a neurologic examination revealed congenital bilateral optic atrophy, tapetoretinal degeneration, myopia, secondary epilepsy and psycho-motor retardation, she was directed to take mephenytoin and phenobarbital. After a week the child developed 40 °C fever and skin efflorescences all over the body, accompanied by restlessness and vomiting.

On admission morbilliform rash was noted on the face, neck and extremities. Soon blisters appeared, coalescing rapidly into large foci. Management consisted in topical treatment as for burns. On the third day after admission, mephenytoin as

TABLE I
Serologic tests in Case No. 1

Drugs	Complement fixation	Passive haemagglutination	Immuno-diffusion [11]	Indirect basophil degranulation test [13], per cent
Sulphametoxydiazine	neg	0	neg	26
Sulphadimidine	neg	0	neg	2
Erythromycin	+	0	neg	22
Tetracycline	+	0	neg	44
Acetylsalicylic acid	neg	1 : 8	+	52

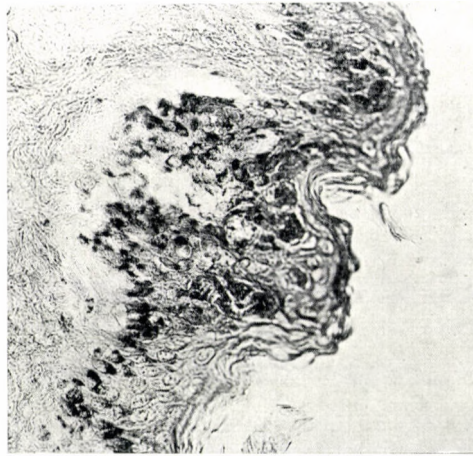


FIG. 1. Irregular distribution of melanin in degenerating basal cells and malpighian layer

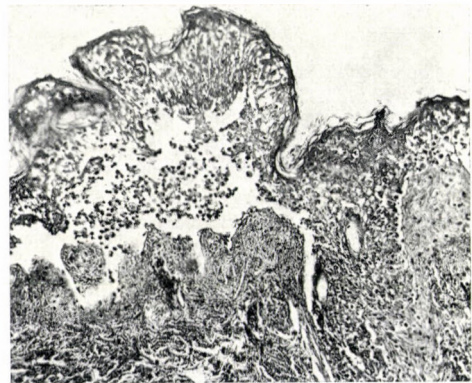
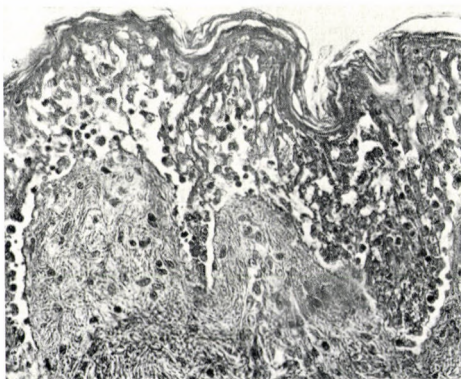


FIG. 2. Necrosis of the whole epidermis; in the adjacent dermis, increase of histiocytes and some mononuclear cells

FIG. 3. Subepidermal blister filled by polymorphonuclears, histiocytes, proteinaceous fluid and necrotic debris

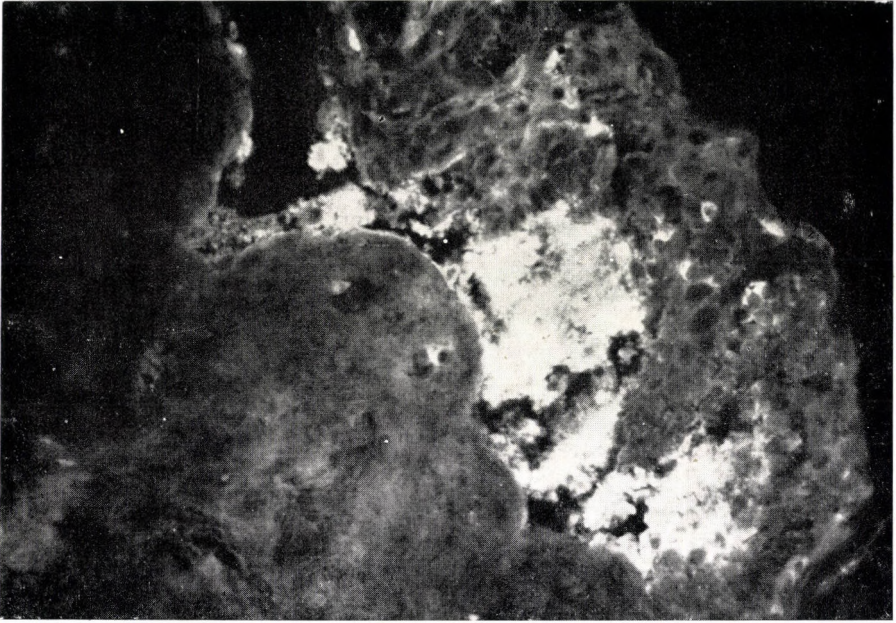


FIG. 4. Section of skin treated with fluorochrome-conjugated antibody to human serum albumin revealing bright fluorescence in subepidermal blister

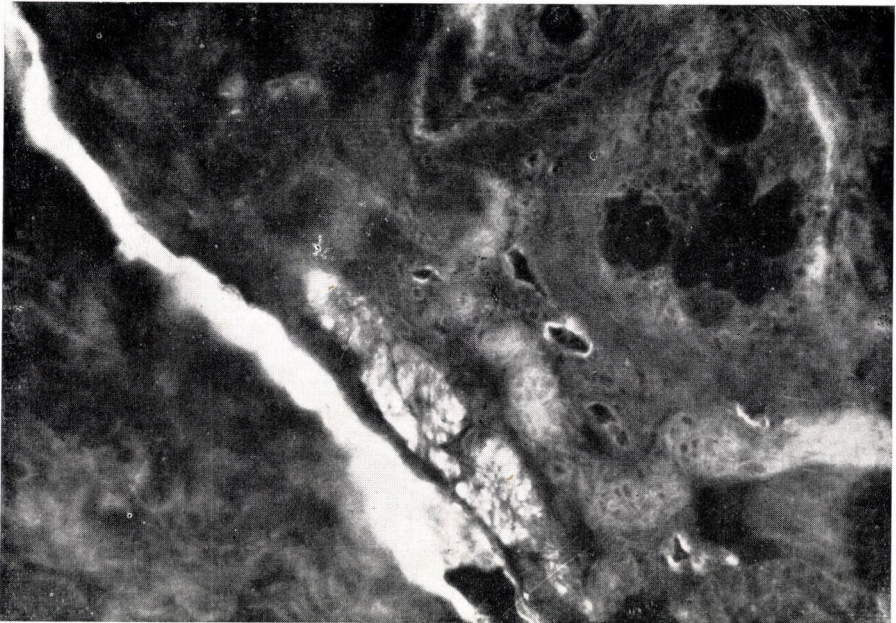


FIG. 5. Fluorescence within and along a dermal vessel in a section treated with antibody conjugate to human IgG

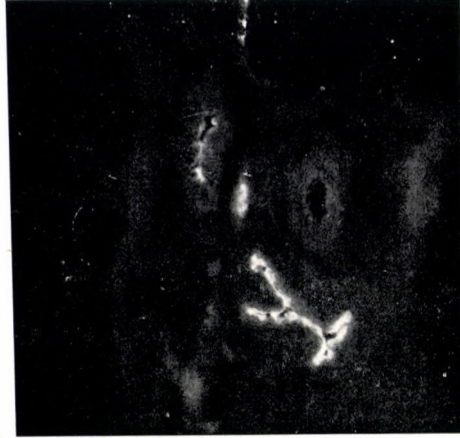


FIG. 6. Section of derm treated with antibody-conjugate to human IgM. Immunoglobulin fluorescence in the vessel and capillary walls

one of the possible causative factor was discontinued, but the child continued to take acetylsalicylic acid that had been administered ever since the first bout of fever in a dose of 0.15 g t.i.d., together with tetracycline, phenobarbital, and vitamins A and B₂.

Laboratory results were, ESR, 13/20; Hb, 10.4 g per 100 ml; RBC, 4,030,000; WBC, 2000; differential count: neutrophils, segmented 51%; unsegmented 1%; eosinophils 2%; lymphocytes 42%; monocytes 4%.

The condition could not be relieved. The child died in coma with cardiac failure on the 11th day after the onset of the rash.

Necropsy revealed catarrhal desquamative pneumonia; acute pharyngitis with abundant Gram-positive organisms; a fatty liver with vacuolized nuclei of hepatocytes; in the kidneys, thickening of the glo-

merular mesangium and of the arteriolar walls which were PAS-reactive; and in the brain, diffuse gliosis, demyelination of the optic nerves and small foci of malacia in the pons.

Histologic examination of the skin. The changes were essentially similar as in the preceding case, with necrotic epidermis, thickened and homogeneous collagen fibres. The dermal vessels were dilated and obstructed with haemolysed erythrocytes and thrombocytes. Around the vessels moderate lymphocytic and histiocytic infiltrations with sparse polymorphonuclears were noted. On the surface of the necrotic epidermis and the denuded derm, Gram-positive organisms were found in clusters.

Serologic tests for drug sensitivity were carried out in postmortal serum. Results are shown in Table II.

TABLE II
Serologic tests in Case No. 2

Drugs	Complement fixation	Passive haemagglutination	Immunodiffusion	Indirect basophil degranulation test [13], per cent
Erythromycin	neg	0	neg	18
Mephentyoin	+++	0	neg	0
Acetylsalicylic acid	++	0	+	2

DISCUSSION

In the origin of Lyell's syndrome a combination of several drugs along with some infection are believed to play a part, modifying the renal and hepatic functions responsible for the degradation of drugs. The antigenic effect of one and the same split product may vary in dependence on age, enzymatic disturbances, or on the readiness of the immune system to respond in a special way to different antigenic stimuli [1, 4].

In our cases acetylsalicylic acid has probably played a significant part, in the first case in combination with sulphonamides and antibiotics, in the second case with mephenytoin. This assumption has been supported by the serologic findings.

In this regard, acetylsalicylic acid was taken into account by Lyell [10], and several other authors [4, 8, 12, 15]. Acetylsalicylic acid may undergo an acetylation reaction with body proteins; the reaction is decisive of changes in platelet aggregation, and commercially contaminated preparations with highly reactive acetylsalicylic anhydride may be responsible for the immunological effects [7, 16, 17].

Using the immunofluorescent staining technique we have demonstrated in both cases immunoglobulins in cutaneous lesions, and serologically antibodies to drugs, most convincingly to acetylsalicylic acid. These findings must, however, be judged guardedly since the presence of immunoglobulins does not yet prove the involve-

ment of antigen-antibody complexes; nor do the serological tests prove that they were antibodies with reaginic activity, especially as the first patient had adrenocortical therapy.

In the case observed at this Department in 1963 [12] we were already considering the eventual role of acetylsalicylic acid in enhancing the violent progress of epidermal necrolysis in a girl of 4 years. It is noteworthy that most cases of Lyell's syndrome with previous acetylsalicylic acid intake occurred in childhood [8, 12, 15], and according to Eriksson [6] children are more sensitive to salicylate than are adults.

It is assumed that acetylsalicylic acid besides its toxic effect might have acted in both of the present cases by a pathomechanism based on an antigen-antibody-linked immune response. The antibodies to acetylsalicylic acid demonstrated serologically offered support to that assumption.

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