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Toxic Epidermal Necrolysis (Lyell Syndrome) and its Medico-Legal Implications

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Summary. The authors describe toxic epidermal necrolysis and report on the clinical observation and post mortem findings in a 5 year old girl, treated with monophenylbutazone. The correct diagnosis is important since the changes might otherwise be wrongly ascribed to burning. The diagnosis also raises the question of a therapeutic mishap and, in turn, the possibility of a claim for compensation.

Zusammenfassung. Bericht über einen Fall von Lyell-Syndrom (Epidermolysis toxica acuta). Fünfjähriges Mädchen entwickelte 2 Tage nach Aufnahme von 5mal 100 mg Monophenylbutazon (in Westdeutschland nicht im Handel) ein Exanthem aus kleinen roten Flecken. 2 Tage später erschienen klare Blasen, und schließlich ließ sich fast am ganzen Körper die Haut in großen Fetzen ablösen. Tod bei Hypothermie und zunehmender Bewußtseinstrübung 18 Tage nach Beginn der Erscheinungen. Die Sektion ergab u. a. makroskopisch Bronchopneumonie, Mediastinalemphysem, Hirndruck, Stauungsorgane; mikroskopisch leichte Leberverfettung, toxische Schwellung der Milzkeimzentren, Entspeicherung der Nebennierenrinde; bakteriologisch: Pseudomonas aeruginosa. Die Eltern beschuldigten Ärzte und Apotheker der falschen Behandlung. Fälle dieser Art können irrtümlich als Verbrennung angesehen oder als therapeutische Unglücksfälle mit allen möglichen rechtlichen Konsequenzen gedeutet werden.

Key words: Lyell-Syndrome — Toxic Epidermal Necrolysis.

Without doubt, one of the most dramatic diseases which still has a fatal outcome is the syndrome of "Toxic epidermal necrolysis" described by Lyell in 1956 [8]. Several cases had, in fact, been described earlier and can now be brought under the same heading.

It takes the form of a sudden and dramatic generalized skin eruption followed by extensive epidermal loss. There ensues in a short time a typical picture which has been variously described as: "picture of heavy scorches" (Rook), "flayed alive" (Degos), "plunged in boiling oil" (Griveaud), "scalded" (Garnier, Bureau, Kaplan) [6]. The picture is very similar to the one seen in post-mortem kerosene contamination and mentioned in 1970 by Wilkinson [18] in his exhaustive work on the differential diagnosis of the syndrome. We have often seen it in victims of aircraft crashes.

The symptoms make their appearance either suddenly, or following a commonplace prodrome suggesting pyogenic or viral infection. It seems justified to attract the attention of medico-legists to the syndrome because of its high mortality

rate (15) and fulminating course. It is generally accepted that, in the period 1938—1966, nearly half the patients died. Massé [10] is even more pessimistic and speaks of a death rate of two thirds, whereas Reich [13] puts it at 20 to 30%. Bruneau-Decelle and Ledoux-Corbusier [2] have come forward with the reassuring news that a better knowledge of the disease and of its therapy has considerably improved its prognosis and they advance a present day mortality risk of hardly more than 10%. Lyell in his review of 128 cases finds an over-all mortality of 23% [9]. The clinical picture can be summarized as follows. Either suddenly or after a short illness there occurs a generalized erythema followed rapidly by the loss of the dermo-epidermal adherence. This leads to the formation of extensive blisters which tend to enlarge rather than to burst. Massive epidermal detachment is conspicuous. The sign of Nikolsky (by which is meant skin-shedding at the slightest touch of the finger) is present. Sometimes one is even confronted with what Lamy (1964) calls "the sign of the glove finger": the epidermis of the fingers of the whole hand can readily be pulled off. The dermis is now bare, red and painful. Exudation ensues and eventually infection. Up to 80% of the mucosal surface can also be involved in the process, especially in staphylococcal cases (9). The temperature can rise up to 104°F and a condition of shock progressively sets in. At a later stage, even the fingernails can fall off. Death frequently follows within 10 to 12 days. If recovery takes place the skin will regenerate but scars remain and also, quite often, there are ophthalmic sequelae (5). Germain *et al.* [3] attempted recently to deal with the latter by corneal grafting but were unsuccessful. A peculiarity of the Lyell syndrome is its greater frequency in females, often girls. Most instances are to be found in individuals either under 15 or over 40. The cause of this syndrome is as yet unknown. Several suggestions have been made and at present the most favoured explanation is that the changes are an allergic reaction to drugs. This list of drugs alleged to have been responsible is lengthy (16) but we mention only the following:

— sulphonamides, including those with a delayed action and those causing hypoglycemia;

— aspirin and antipyretics (phenacetin, etc.);

— pyrazolone — pyramidon — phenylbutazone, etc.;

— penicillin — streptomycin — chloramphenicol — tetracyclin.

The many drugs which have been implicated are remarkable by their chemical diversity and lack of structural similarity. Indeed, the only feature they have in common is their wide use as palliatives in anti-phlogistic and anti-pyretic therapy, according to the practitioner's personal choice. Delayed action sulphonamides are considered the main culprits. Non-pharmaceutical substances such as fish, berries, kerosene and DDT [4, 12] have also been implicated. The theory of allergic reaction, however, must account for the fact that many patients given these drugs do not develop this syndrome. Most of the drugs are prescribed, rightly or wrongly, at the onset of an unidentified infection. This raises the alternative possibilities: did the drug cause the syndrome, or was the illness one which began as a vague mild infection but which suddenly developed in a dramatic fashion, and for which the drug was in no way responsible (Bruneau-Decelle and Ledoux-Corbusier [2]). In other words, the syndrome is due to an infection. The first symptoms to appear are often of an infectious character; frequently there

is high temperature and, later, localisation to the lungs. Bacteriologic and virologic studies have nevertheless brought no convincing support to this view, though the finding of staphylococcus [11, 17] and pseudomonas is recorded. Lyell [9] and Samuels [14] underline staphylococcal infection as a predominant feature. An enzymatic theory has also been advanced. According to Lebioda [7], there may be a genetic eliminatory dysfunction at the level of the epithelial cells of the skin and a consequent necrosis of the latter, because of disturbances in their biochemical pathways.

Case Report

A 5 year old girl was admitted to the Childrens' Department at the Medical School on the 8th of December 1969 with an extensive bullous dermatosis. 2 months previously she had had bronchitis and still coughed occasionally. 10 days prior to admission she had started complaining of vague headache and nausea. Her father had noticed pustules in her throat and had taken her to an oto-rhino-laryngologist who had prescribed the following powder:

R/Monophenylbutazone	100 mg[1];
Phenylephrine	3 mg;
Diphenylhydramine	7 mg.

The patient had taken 5 of these when, in 2 days time, an exanthema made its appearance; this took the form of small red spots on the face and neck and extended the next day to the whole surface of the body. Itching ensued and, after 2 days, small clear blisters made their appearance and became progressively larger. The girl was not feeling well and complained of pain. The paediatrician at first thought it was a case of measles but revised this diagnosis as the illness developed. The child was admitted to a hospital on the 3rd of December. She stayed there 5 days, when the parents were then warned that her life was in danger. On their own initiative, they thereupon transferred her on the 8th of December to the Childrens' Hospital at the Medical School. On admission, the patient was dehydrated and severely ill. She was conscious and complained of severe pain. The surface of the body, especially the trunk and the upper limbs, was the seat of large red patches following shedding of the epidermis; fluid oozed from these patches. Blisters, either filled with clear fluid or ruptured, were still present in some

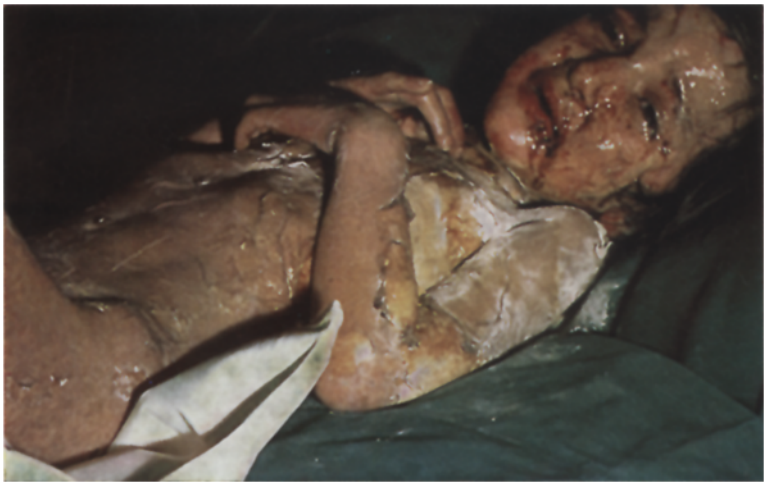

Fig. 1. Condition of patient on 10. 12. 1969

1 Monophenylbutazone is not available commercially in Western Germany.

places. Large leaves of epidermis could be stripped off easily; Nikolsky's sign was strongly positive. The face was involved but not the scalp. Blepharitis and conjunctivitis were present. The legs, especially the lower parts, were less affected; only, brownish patches were present and these were considered to be sequelae to a macular exanthema. The clinical condition was poor. Lung auscultation revealed humid ronchi. The body temperature did not exceed 99°F. The peripheral blood picture indicated an infection:

Leucocytes	12000 per cubic millimetre
Stab cells	38%
Segmented neutrophils	28%
Lymphocytes	26%
Metamyelocytes	6%
Atypical lymphocytes	2%

The blood electrolytes, urea and creatinine confirmed dehydration. There was albuminuria and glucosuria. Cultures from blood, skin and faeces revealed no pathogenic bacteria.

The patient was nursed under sterile conditions with local application of Vioform and Nebacetine. The general condition was treated with Keflin, Soludacortine, Digitaline; electrolytes and fluid were kept balanced. After 2 days, shedding of the epidermis was generalized except for the scalp and the lower part of the legs. The back was entirely deprived of epidermis and the bleeding dermis was exposed. The eyelids were swollen and the lashes fell out; the eyebrows were also involved. The mucosa of the mouth, nose and throat began to bleed and desquamate, with tenacious mucus adhering to it. Catheter feeding was difficult to maintain because the patient reacted to it by foul-smelling diarrhoea. The general condition worsened progressively and oedema appeared. On the 18th of December 1969, the patient became agitated and unconscious. Hypothermia (92°) and, a few hours later, cardio-respiratory collapse occurred, resulting in sudden death, 18 days after the onset of the symptoms. Autopsy was performed on the 21st of December 1969.

The body was that of an emaciated girl measuring 112 cm and weighing only 17 kg. The trunk, the upper limbs, the neck and the thighs were almost entirely covered by yellowish crusts with underlaying granulation tissue. The skin of the face was brownish and indurated. In some places, most particularly the right hand, the necrotic epidermis could readily be stripped off. In short, the appearances, except for the legs, were identical with those of a burned body. An incision into the back revealed obvious oedema of the lumbar region. There was slight mediastinal emphysema. The left lung weighed 130 g; the right 190 g. There was discrete bronchopneumonia. The heart was normal and weighed 110 g. The liver was not enlarged but was slightly congested; its surface was smooth and it weighed 360 g. The spleen was firm and weighed 46 g. The suprarenals were of approximately equal size and weighed 2 g each. The kidneys were slightly congested with a normal cut surface. The left kidney weighed 70 g; the right 64 g. The intestinal tract was ballooned, pale and mostly empty. The stomach contained a little watery mucus. The meninges were oedematous. The brain weighed 1280 g and was healthy. A moderate pressure cone was present.

Histology

The heart muscle showed a normal structure. The liver showed slight fatty change and was congested. Both kidneys were normal except for a slight amount of coagulated matter in the convoluted tubules. In the spleen, the germinal centers of the Malpighian bodies were markedly swollen, producing the picture of the so-called toxic bodies. The suprarenals showed depletion of the cortical lipoids and were markedly congested. The medulla was lacunar and many nuclei were pyknotic both in the cortex and medulla. The lungs showed foci of bronchopneumonia with local necrosis of the parenchyma and accumulation of mononuclears and lymphocytes.

The skin of the face was denuded of epidermis. The superficial corium was necrotic with many pyknotic nuclei; underneath, the capillaries were dilated, and

the hair follicles and sweat glands had vanished. The fat lobules of the sub-cutis had remained intact. The skin of the abdomen showed similar alterations.

Here, however, hair follicles were still present in small numbers and the sweat glands had escaped damage. A few lymphocytes and histiocytes surrounded dilated capillaries and were present in abnormal numbers in the sub-cutis.

Bacteriology

Bacteriological investigations of the throat, the cerebro-spinal fluid, the pericardial fluid, the gall-bladder and the lungs produced pseudomonas aeruginosa in all sites.

Discussion

The clinical picture, the exhaustive investigations carried out in the Childrens' Hospital and the post-mortem findings all corroborate the diagnosis of toxic epidermal necrolysis. This condition, fortunately, is rare but it has important medicolegal implications. It may be wrongly diagnosed as a case of severe burns and thus raise the issue of accidental or criminal causation (Massé [10]).

It may be regarded as a grave therapeutic mishap [1] and bereaved relatives may be prompt to allege negligence. Indeed, this view may be shared by those then entrusted with the indivious and always delicate task of assessing responsibility. In the present case allegations of negligence involved the rhino-laryngologist, the pharmacist and the first hospital. The medico-legal report, however, absolved them from liability.

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