Multiple Bullae and Paresis after Drug-induced Coma
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Two cases of bullous skin lesions and paresis following coma due to the ingestion of many antipsychotic drugs were reported. Histological examination showed an intra-epidermal blister in case 1 and degeneration of sweat glands in both cases. An immunofluorescence study showed massive deposits of IgM and C3 in the dermal vessels. As similar deposits of immunoglobulin and complement were not observed in patients with ordinary lesions such as decubitus, a different mechanism in the formation of the bullous skin lesion other than pressure is suggested. Key words: Blister; Drug-overdosage; Immunofluorescence; Sweat gland.

(Accepted April 22, 1991.)
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Bullous skin lesions associated with drug-induced coma were in the past termed 'barbiturate burn marks' (1), because barbiturates were used in suicidal attempts on many occasions and these skin lesions were first noticed in association with a barbiturate overdosage. Since 1970, other narcotic drugs have been reported to cause this type of skin lesion too (1, 2). We have recently seen 2 patients who were in a coma as a result of taking many antipsychotic drugs and who showed characteristic skin lesions after recovery. As there are only a few reports in which direct immunofluorescence study was performed on biopsy specimens from such patients and these results differed considerably, we describe the clinical findings and direct immunofluorescence findings of this skin disorder.

CASE REPORTS
Case 1
A 40-year-old man was referred from the mental clinic for the evaluation of bullous lesions of 4 days' duration on his arm and thigh. He also complained of the numbness and swelling of his right arm. He had no special familial history or previous disease except for an atypical psychosis for which he had been treated in the mental clinic for 2 years.

On examination, several clearly defined bullae on an erythematous base with an irregular border were found on the occipital region, the right shoulder, the right arm (Fig. 1), the right thigh and the dorsal side of his left fingers. Several rectangular red plaques were also seen on his right chest. Most lesions were situated over the bony prominences. He had been in a comatose condition for 40 h in his home after ingesting numerous antipsychotic drugs, namely, tricyclic antidepressants (35 tablets of Nor triptyline-HCL, 14 tablets of Amitriptyline-HCL, 12 tablets of Imipramine-HCL), Benzodiazepines (20 tablets of Nitrozepam, 6 tablets of Lorazepam, 6 tablets of Metazepam, 2 tablets of Clonazepam, 2 tablets of Cloral, 4 tablets of Cloridiazepoxide and others (6 packs of 0.2 g barbiturate, 4 tablets of sulpiride, 2 tablets of lithium carbonate). After awakening, he presented several skin lesions and complained of the numbness of his right arm. He was treated initially with 30 mg of prednisolone orally for 4 days. The edema of the right arm and the hand subsided completely within 8 days and the skin lesions disappeared within a month. But the paresis of the right ulnar and median nerve did not improve even after 2 months.

Case 2
A 23-year-old female clerk was also referred from the mental clinic for bullous lesions of 5 days' duration on her thigh and legs. She had no familial or previous history except for schizophrenia which had been treated for 6 months. On examination, egg-sized bullae were seen on the right thigh and bilaterally on the sides of her soles. She also complained of numbness in the right leg and foot. After she had tried to commit suicide by taking many drugs 6 days earlier, she had been in a coma for 4 days in an intensive care unit, with hemodialysis. Her family reported that she took 20 tablets of Levomepromazine maleate, 86 tablets of Broma-
zepam, 70 tablets of Bromperidol and 66 tablets of Biperiden-HCl. All blisters disappeared within a month, except for the blister on the right thigh which became a deep ulcer and needed an operation 2 months later. The paresis of the right peroneal and plantar nerve did not improve even after 3 months.

MATERIAL AND METHODS
Two biopsies were taken from the border of the bulla on the right arm in case 1 and the erythema around the blister of the right thigh in case 2. Paraffin-embedded, 5 μm thick sections were stained with hematoxylin-eosin and PAS. For direct immunofluorescence microscopy, 6 μm thick cryostat sections of the fresh-frozen tissue were stained with fluorescein-conjugated antisera against human IgG, IgA, IgM, C1, and fibrinogen (Behringwerke, Germany). Tests were repeated three times and appropriate blocking slides and unstained controls confirmed the specificity of the fluorescent staining.

RESULTS

Light microscopic findings
The biopsy specimen from the bullous lesion in case 1 revealed an intra-epidermal blister with a necrotic epidermal roof and re-epithelialization (Fig. 2). Slight intercellular edema of the lower part of the epidermis was observed in case 2. Both patients showed slight edema and dilatation of the capillaries but without accumulation of inflammatory cells in the upper part of the dermis. Cellular degeneration characterized by an eosinophilic homogeneity of the cytoplasm was seen in the follicular epithelium (Fig. 3A) and secretory cells of the eccrine sweat gland (Fig. 3B) in case 1. Patient 2 showed moderate degeneration of the secretory cells of the eccrine sweat glands.

Direct immunofluorescence study
The direct immunofluorescence study showed the presence of moderate intercellular deposits of IgG, C1, and fibrinogen in the epidermis in case 1. No deposition in the epidermis was seen in case 2. Massive granular deposits of IgM and C1 were seen in the upper dermal vessels of both cases. Also heavy linear deposition of fibrinogen in the dermal vessel was observed in case 1. There was no deposit along the basement membrane zone.

DISCUSSION
Our patients showed characteristic bullous skin lesions and paresis after coma caused by the ingestion of more than 100 tablets of antipsychotic drugs. Characteristic bullous skin lesions among comatos patients have been reported mainly since 1950. In 1952, Holten (3) described 501 cases of acute barbiturate poisoning, in which 4% had bullous lesions. Beveridge & Lawson (4) found bullous skin lesions in 19 of 240 patients with acute barbiturate poisoning (6.5%). Recently other drugs also have been reported to produce similar lesions: Diazepam, Chlorpromazine, Amitriptyline-HCl, Clorazepate dipotassium, Methadone, Hydrocodeine bitartrate, Meperidine, Imipramine-HCl, Acetylcarbromal, Glutethimide, Methyprylon (1, 2, 5–7). The pathogenesis of these lesions is still obscure. Bie & Kirkgaard (8) are convinced of a traumatic origin. Mandy & Ackerman (9) believed that the lesions were produced by hypoxia coupled with trauma. Some authors (3, 5) feel that pressure alone cannot possibly explain all these phenomena. Our immunofluorescence study demonstrated the intercellular presence of IgG, C1, and fibrinogen in the epidermis of case 1, and IgM and C1 in the dermal vessels of both cases. Reilly & Harrington (10) recently reported a similar case of positive direct immunofluorescence, with patchy intercellular staining for IgG, IgM and C1 in the epidermis with fibrinogen deposition along the basement membrane. Rocamora et al. (11) also reported a similar case of positive direct immunofluorescence study with IgM and C1 deposits in the dermal vessel. Intercellular deposits of immunoglobulin and complement in the epidermis might be nonspecific changes, as the roof of the blister in case 1

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showed necrosis, while the other patients, who had slight intercellular edema of the epidermis, demonstrated no such deposits. Histologic changes in early stages of decubitus or pressure sores resemble the tissue findings of the bullous lesion in comatose patients, including sweat gland and duct necrosis (12). But immunofluorescence findings in 5 cases of decubitus showed no deposits of immunoglobulin or complement in the basement membrane zone and dermal vessels (12). As decubitus is caused by pressure alone, the deposition of immunoglobulin and complement in the dermal vessels suggests other mechanisms of blister formation in drug-induced comatose patients. Further studies are needed to understand the mechanism of this disease.

REFERENCES

Seborrheic Dermatitis and Daylight
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Patients with mood depression have been found to have a higher prevalence of seborrheic dermatitis (SD), possibly related to their tendency to live indoors. The prevalence of outpatients with SD has now been found to be directly related to the number of gloomy days in the area. Since UV light might not be the only reason for the well-known improvement in SD in summer, an explanation possibly related to melatonin is envisaged.

(Accepted May 29, 1991.)
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Patients with mood depression have been found very recently to have a high prevalence of seborrheic dermatitis (SD) (1). To explain such a relationship, the well-known beneficial role of sunlight on SD has been recalled: depressed patients, like neurologic patients prone to develop SD, tend to live indoors, avoiding sun exposure (1).

We studied the possible relationship between sunlight and prevalence of SD.

PATIENTS AND METHOD
The SD outpatients who attended our Department in 1989 for a first visit were registered each month and their prevalence over the whole outpatient population was compared with the average number of gloomy hours per day per month in the Genoa area as obtained from the Azienda Autonoma di Assistenza al Volo at Genoa Airport. The gloomy hours were those in which the sky vault was entirely covered by clouds and included the hours after sunset.

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