THE JOURNAL OF INVESTIGATIVE DERMATOLOGY
Vol. 60, No. 5

Printed in U.S.A.

BULLAE: A CUTANEOUS SIGN OF A VARIETY OF NEUROLOGIC DISEASES*

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ABSTRACT

Bullae, erosions, red-blue plaques, and macular erythema are commonly found on sites of pressure in patients immobilized for prolonged periods. Coma from drug overdose is the most frequent predisposing event, but the lesions cannot be related to the toxic effects of any specific medication. The cutaneous lesions are a result of pressure-induced ischemia (and anoxia); their histology may include subepidermal bullae and focal necrosis of epidermis, dermis, subcutaneous tissue, and all epidermal appendages.

Since Napoleon's time, blistering and erosive cutaneous lesions have been seen in severely ill and comatose patients. During the occupation of Berlin in 1806, Larry, the Emperor's surgeon, noted such lesions over pressure points in soldiers comatose from carbon monoxide intoxication [1]. Recently, the possible diagnostic significance of bullous lesions as specific cutaneous stigmata of barbiturate-induced coma [2] has focused renewed attention on skin lesions in severe drug overdose. In this communication we will prove, on the basis of our recent clinical and histopathologic experience, that these lesions are a result of pressure-induced tissue changes in patients with a variety of neurologic conditions, and are not caused by a toxic effect of any specific drug or its metabolites.

CASE REPORTS

Clinical and histologic data on seven patients demonstrating bullae in association with drug-induced coma are summarized in the Table.

RESULTS AND DISCUSSION

Clinical Findings (Figs. 1, 3, 4)

In these cases the cutaneous lesions consisted initially of blanchable erythematous macules which then either progressed to red-blue plaques and sometimes to bullae and erosions, or subsided spontaneously. At times all stages were seen simultaneously in the same patient. Bullous and erosive lesions often were followed by scar formation. The distribution of lesions invariably corresponded to sites of maximum pressure.

Histologic Findings (Figs. 2, 5–10)

The slides studied were from the patients above, as well as three cases supplied by Drs. G. W. Beveridge and E. Brehmer-Andersson [3, 4]. All specimens demonstrated bullae roofed by a partially to frankly necrotic epidermis. At the edge of bullae the basement membrane regions often appeared indistinct [5]. The papillary dermis beneath the bullae stained either brightly eosinophilic or faintly basophilic and demonstrated an homogeneous often edematous granular appearance with pyknotic nuclei scattered in the involved regions.

The sweat glands and ducts appeared almost uniformly necrotic with pyknotic or ghost-like nuclei, a finely granular, brightly eosinophilic cytoplasm, smudged cell membranes, and an indistinct, finely granular basement membrane region. An acute inflammatory infiltrate surrounded and often invaded the altered structures.

The pilosebaceous units were almost uniformly affected in all specimens, with frequent sebaceous gland necrosis (Fig. 5), occasional necrosis of the external and internal root sheaths, and hemorrhage into a hair papilla in one specimen (Fig. 9).

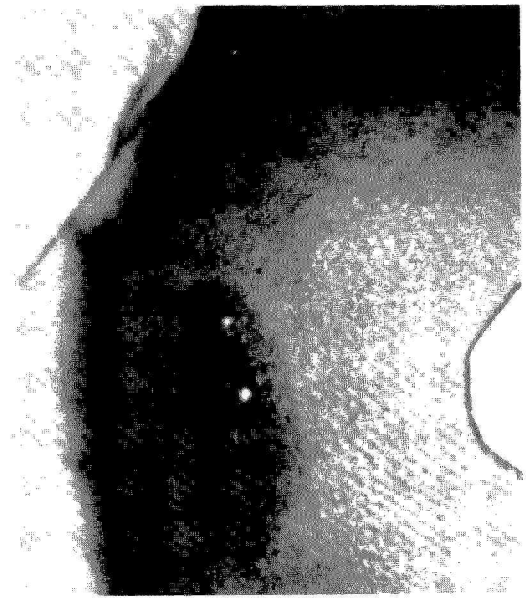

FIG. 1. (Case I) Blisters with sharp margins arising in an edematous plaque on the deltoid area of the shoulder.

Manuscript submitted November 28, 1972; in revised form January 17, 1973; accepted for publication January 18, 1973.

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† Supported in part by Grant AM 06183, U.S.P.H.S.

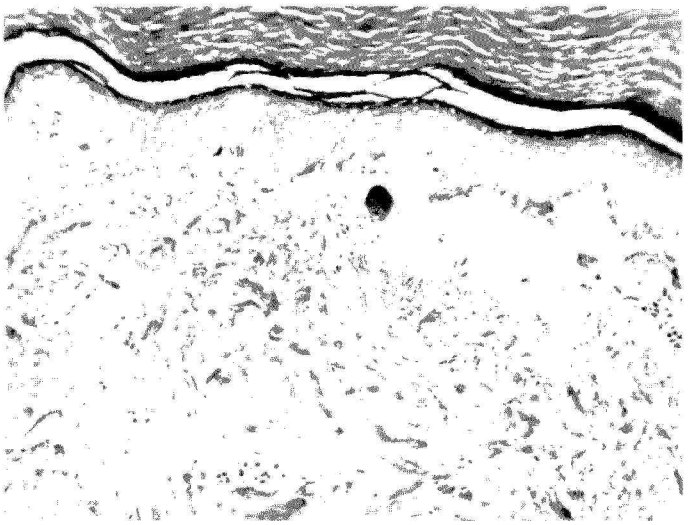

FIG. 2. (Case II) Focal necrosis of the epidermis overlying a subepidermal bulla. Fibroblasts in the upper dermis appear pyknotic. × 130.

FIG. 3. (Case III) Linear bullae over the left fifth metacarpal.

In two specimens the arrector pili were necrotic (Fig. 10). Polymorphonuclear leukocytes were dispersed in and about pilosebaceous structures as well as sweat glands.

Intense eosinophilia of endothelial cells and pyknosis of nuclei were consistently observed in both superficial and deep dermal vessels. In addition, the smooth muscle layer of several large vessels demonstrated pyknotic nuclei, an homogeneous granular appearance, intense eosinophilia, and focal invasion by polymorphonuclear leukocytes. Hemorrhage was present about involved vessels.

Subcutaneous tissue exhibited focal areas of necrosis, edema, and acute inflammation.

Etiologic Agents

CO intoxication. The original observations of Larry concerning CO intoxication [1] have since been confirmed by both clinicians and pathologists [6–13]. In 1948 Hedinger [7] noted that muscle and skin necrosis appeared soon after acute CO toxicity, and later peripheral neuropathy was often seen. A spectrum of skin lesions, consisting most commonly of erythema, but also of edema, papules, vesicles, induration, ulceration, and dry gangrene primarily over pressure areas was described by Meigs and Hughes in 31 of 105 patients [8]. The clinical impression was often "burns" despite histories of exposure solely to

TABLE

Case #	Age and sex	Duration of coma prior to admission	Drug(s) ingested and amount when known	Serum level of drugs	Clinical findings and course	Histologic findings
Case I	32 F	24 hr	8 gm glutethemide 200 mg diazepam	glutethemide: 6.5 mg% barbiturate: 0	Erythematous and edematous plaques 2–3 cm diam, surmounted with bullae, on left shoulder (Fig. 1), left forehead, left side of back, and left knee. Traumatic neuropathy with paralysis of left hand became evident on sixth hospital day.	—
Case II	40 F	31 hr	secobarbital	barbiturate: 2.5 mg%	Flacid and tense bullae over both insteps	(Fig. 2) Epidermal necrosis Subepidermal bulla Pyknotic dermal fibroblasts
Case III	46 F	12 hr	15 gm glutetethemide 30 tabs (60–300 gm) diazepam	glutethemide: 2.2 mg% barbiturate: 0	Bullae upon erythematous plaques about left eye, on left ear, left breast, left arm, and dorsum of left hand (Fig. 3)	Epidermal necrosis Subepidermal bulla Focal necrosis of sweat gland epithelium Granular eosinophilic necrosis of endothelial cells of superficial vesicular plexus Fibrin thrombus in a necrotic medium-sized vein Polymorphonuclear leukocytes about involved vessels and scattered throughout the dermis
Case IV	27 F	12 hr	150 mg chlordiazepoxide 600 mg pentazocaine amobarbital and secobarbital	—	Bullae over left lateral malleolus (Fig. 4), erythematous plaque on left knee, erosion in left groin	(Fig. 5) Epidermal necrosis Subepidermal bulla Brightly eosinophilic and homogeneously granular small dermal vessels Necrosis of sweat gland epithelia Necrosis of pilosebaceous apparatus
Case V	20 F	4–24 hr	600 mg secobarbital 24 hr before admission; additional unknown amount 4 hr before admission	barbiturate: 1.6 mg%	Two bullae on opposing surfaces of distal interphalangeal joints of right 2nd and 3rd fingers	—

Case VI	23 F	24 hr	secobarbital prochlorperazine aspirin and other unknown drugs	barbiturate: 1.1 mg% bromide: 6.9 mg% salicylate: 0	Red-blue raised plaques with serpiginous borders, linear erosions, and tense blisters present on right ear, right shoulder, right flank, right dorsum of hand. Marked edema of right eye. A right brachial nerve palsy involving C3, C4 and T1 became evident within 24 hr.	(Figs. 6, 7) Epidermal necrosis Focal necrosis of hair follicles Necrosis of sweat glands and ducts Necrosis of subcutaneous fat Brightly eosinophilic and homogeneously granular endothelium and smooth muscle of a large vein
Case VII	21 M	6–8 hr	glutethemide desipramine amobarbital secobarbital	glutethemide: 4.2 mg% barbiturate: 0.2 mg% salicylate: 0	Bullae and closely grouped vesicles on erythematous plaques on trunk and extremities. Right median nerve palsy became evident on fourth hospital day.	(Figs. 8–10) Epidermal necrosis Subepidermal bulla Necrosis of hair follicles, arrector pili, sweat glands, and sweat ducts

unlit illuminating gas. More recent studies of the pathogenesis of skin and muscle lesions following CO poisoning have implicated pressure ischemia, hypoxia, or both. Howse and Seddon [11] considered that hypoxia rendered tissues more liable to ischemia if they were additionally subjected to ordinarily inconsequential amounts of external pressure. Adams, Denny-Brown, and Pearson felt that muscle necrosis was accelerated by CO inhibition of tissue oxidative enzymes [9]. The occasional delayed appearance of skin lesions in patients with CO intoxication is still unexplained.

Barbiturates. Barbiturates have long received attention as a cause of skin lesions in comatose patients possibly because they have been the most common agents ingested by suicidal patients [14]. Although the overall incidence of skin lesions would appear to be low [2, 15], Adebahr described postmortem skin changes in 50 percent of 149 cases of fatal barbiturate intoxication [16]. Recently Goeschel et al have implied that the presence of bullous lesions was of diagnostic significance in barbiturate poisoning [2].

Other CNS depressants. Bullae have also been reported in comatose patients with overdoses of morphine [17], heroin [18, 19], methadone [19, 20], imipramine [20], acetyl carbromal [20], dihydrocodeine [20], glutethemide [20, 21], methaqualone [22], lysol [23], nitrazepam [24], and amitriptyline [24, 25], as well as in severe hypoglycemic coma [26]. In some of these patients more than one agent had been ingested. Furthermore, we have also seen similar lesions following phenelzine and ethanol overdose. These observations make it highly unlikely that bullae can be utilized clinically to diagnose drug overdose from any specific agent, such as barbiturates. Furthermore, it seems unlikely that these lesions are the result of drug toxicity, since similar lesions have been noted in a variety of CNS diseases.

CNS diseases. Bullous lesions have been noted over pressure points in patients comatose from head trauma [27], following cerebral vascular accidents [28], and in viral encephalitis [28]. In fact, coma itself may not be a prerequisite for the development of these skin lesions since bullous lesions are seen in syringomyelia and have been reported in noncomatose patients with cervical cord ependymoma [29], glioblastoma [30], as an antemortem complication of bilateral prefrontal lobotomy [31, 32], and on the hemiplegic side following a cerebral vascular accident [33].

Immobilization in man and animals. Accidents in humans have produced similar pressure-induced changes. During the London blitz in World War II, people who had been buried or pinned down for two or more hours often developed distinctive erythematous lesions which progressed to blister formation in areas coinciding with sites of prolonged pressure [34]. The most severely affected developed additional muscle and nerve damage. Similar ischemic skin changes

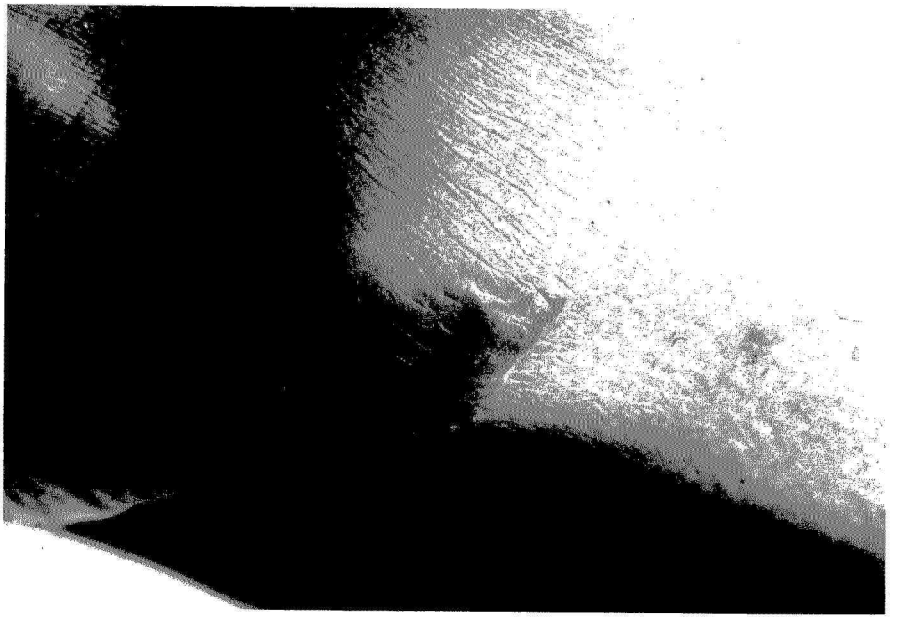

FIG. 4. (Case IV) Sharply marginated bullae confined to the region of the left lateral malleolus.

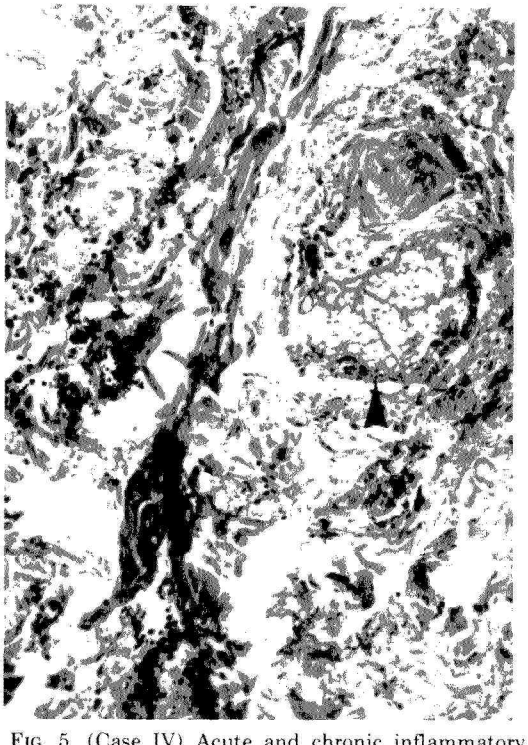

FIG. 5. (Case IV) Acute and chronic inflammatory cells surround and focally infiltrate a necrotic sebaceous gland (arrow) and surrounding dermis. × 140.

have been reported under an overly tight postoperative dressing [35]. In several experiments Kosiak [36] demonstrated that periodic redistribution of pressure over the ischial tuberosities is necessary to prevent irreversible ischemic cellular changes: tissue pressure while sitting on a flat surface (300 mm Hg) was greater than maximum arterial diastolic pressure and far above mean capillary intraluminal pressure (13–32 mm Hg).

Experimental observations in animals substantiate the above observations in humans. Studies in rats [37] have shown that obstruction to circulation was primarily responsible for pressure-induced tissue damage. The duration of pressure was more important than its intensity, and the degree of damage could be strikingly lessened when pressure was applied while tissues were kept at lower temperatures. Experimentally produced pressure lesions in dogs [38] followed an inverse parabolic time-pressure relationship: intense pressure of short duration was equally or more injurious to tissues than lower pressure applied for longer times. Intense pressure resulted not only in cessation of capillary flow but also produced sufficient damage to larger vessels such as venous thrombosis so that ischemia persisted long after pressure had been relieved. The clinical spectrum in animals paralleled that in man: cutaneous ulcers were preceded by edema and hyperemia and histologically there was hemorrhage, cellular infiltration, and hyaline degeneration. In tissues subjected to prolonged pressure, muscle necrosis was observed. Raab [39] induced lesions by compressing limbs of guinea pigs under deep phenobarbital anesthesia. Subepidermal blister formation and exudation, seen after 24 hours, were followed by necrosis and sloughing of epidermis within the following 48 hours.

CONCLUSIONS

The single factor common to all patients with these distinctive cutaneous lesions is prolonged and uninterrupted external pressure. This accounts for several observations, including: (1)

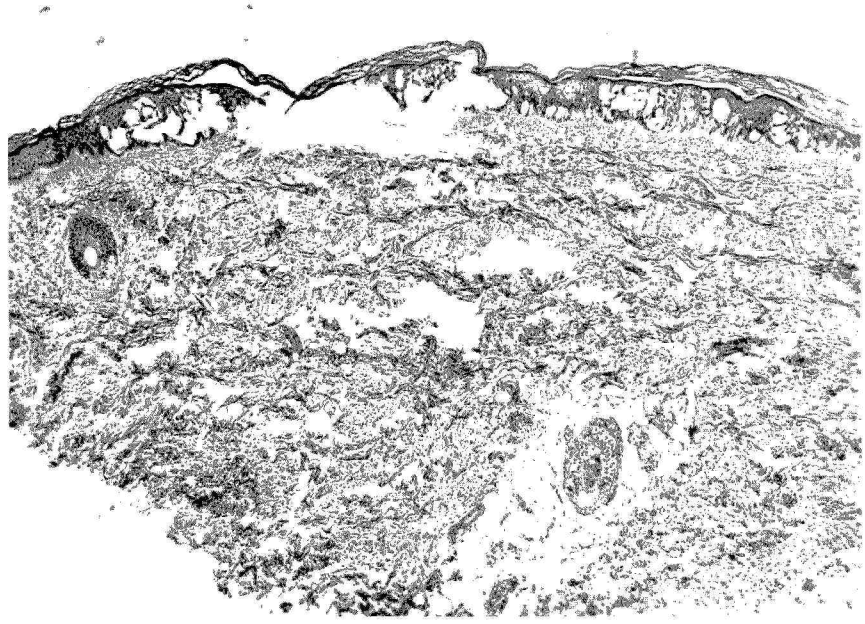

FIG. 6. (Case VI) Extensive epidermal necrosis and focal necrosis of hair follicles. × 48.

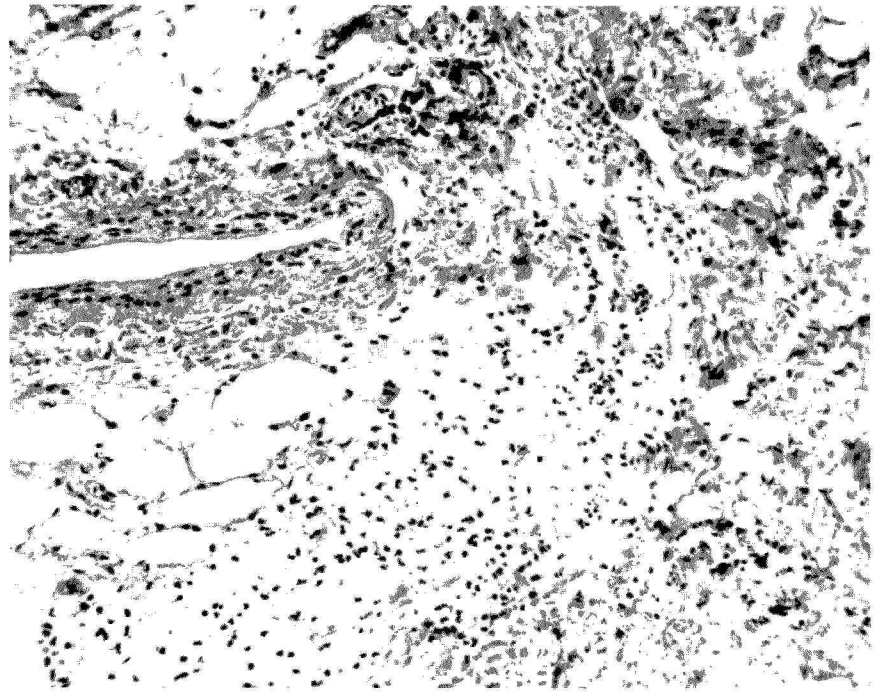

FIG. 7. (Case VI) Edematous and focally necrotic adipose tissue about a large vein is infiltrated by acute inflammatory cells. The endothelium and smooth muscle of the vein stain brightly eosinophilic, are homogenously granular, and have pyknotic nuclei. Polymorphonuclear leukocytes were present throughout the vessel wall. × 160.

frequent appearance over bony prominences; (2) linearity; (3) unilaterality; and (4) localization to sites of bodily apposition. Most patients have a history of neurologic damage which has prevented them either from feeling or responding to stimuli. Thus, pressure-induced local ischemia (and anoxia) seemingly lead directly to tissue injury proportional to the amount and duration of pressure [40] (Fig. 11). Low flow states, induced by shock or vasodilatory drugs, or physical interference with circulation would both accelerate and exaggerate the local insult. If anoxia is presumed

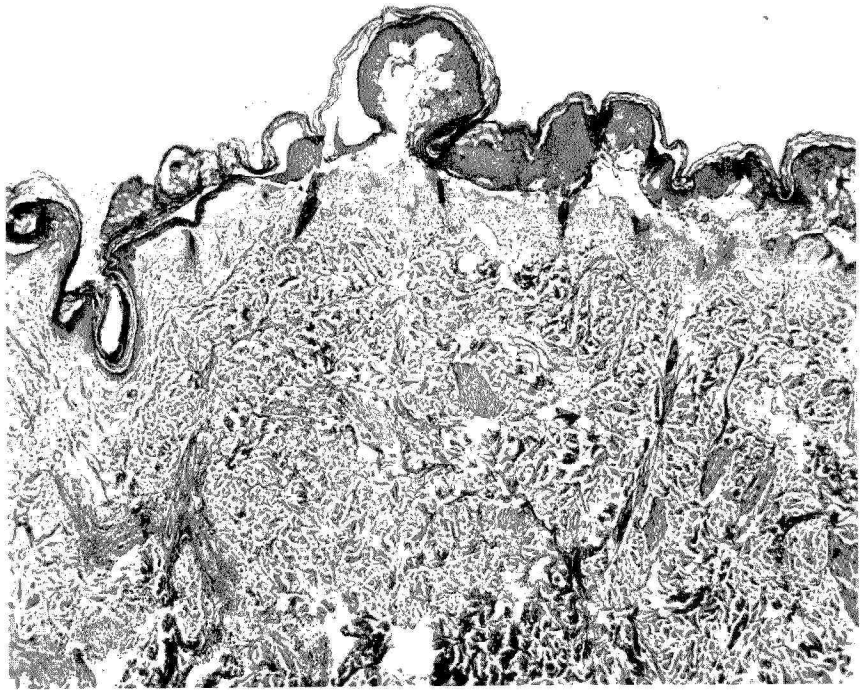

FIG. 8. (Case VII) This subepidermal bulla with necrotic epidermis is associated with necrosis of hair follicles, arrector pili, sweat glands, and sweat ducts. An extensive acute inflammatory infiltrate is present in the dermis. × 43.

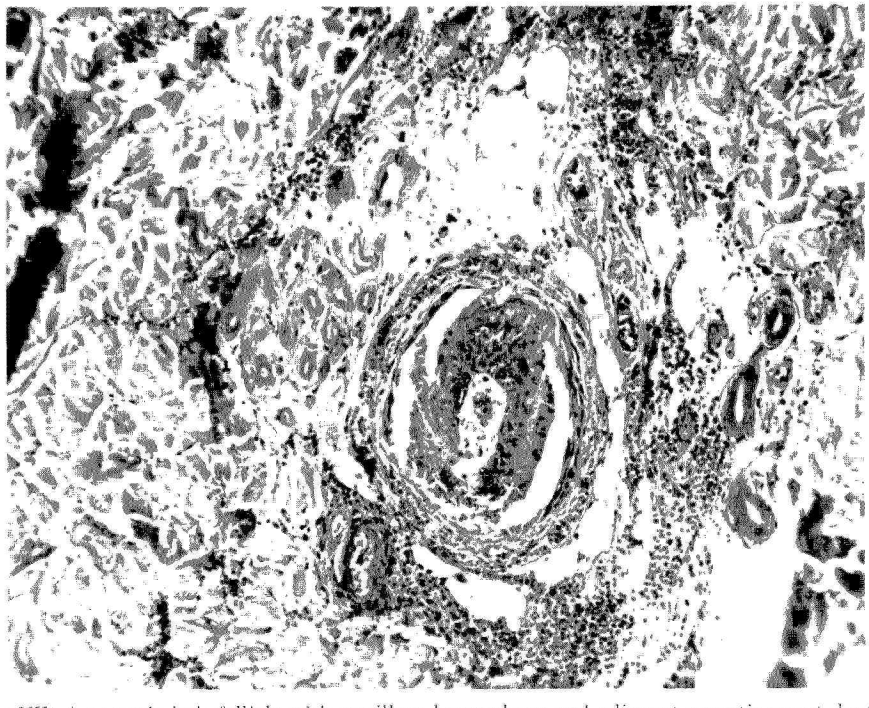

FIG. 9. (Case VII) A necrotic hair follicle with papillary hemorrhage and adjacent necrotic sweat ducts. × 140.

to be the precipitating factor, then the most metabolically active cells would show the earliest and most severe damage.

Previous observers attributed the syndrome to a specific, local toxic effect of barbiturates on the eccrine apparatus because of histologic sweat gland necrosis and the presence of barbiturates in blister fluid and eccrine sweat. This does not explain the now well-documented necrosis of pilosebaceous structures, arrector pili, and cutaneous

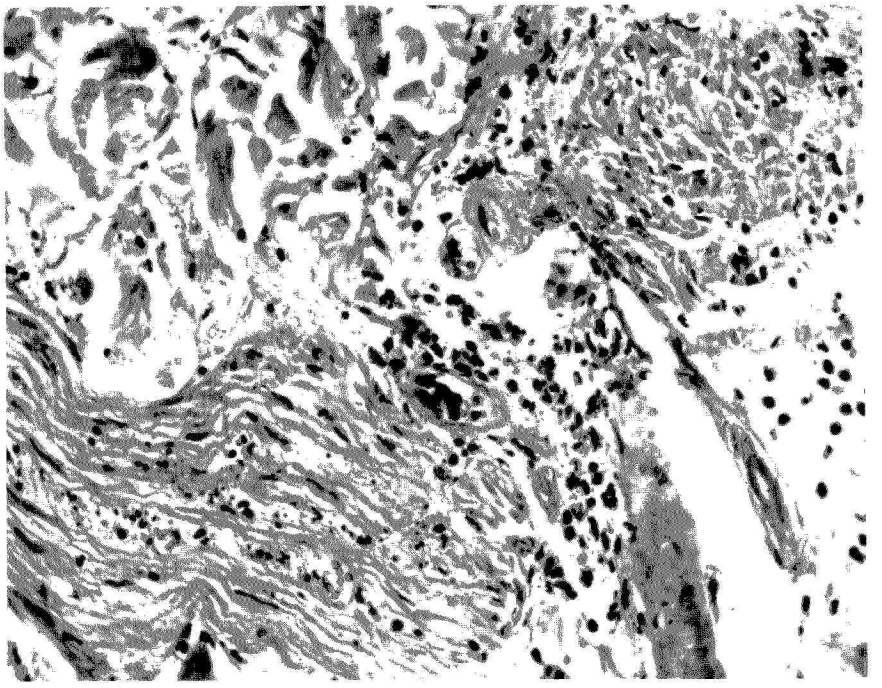

FIG. 10. (Case VII) The arrector pili exhibits smudging of the outline of smooth muscle cells and pyknosis of nuclei. Polymorphonuclear leukocytes and nuclear debris are scattered about and within the altered muscle. × 240.

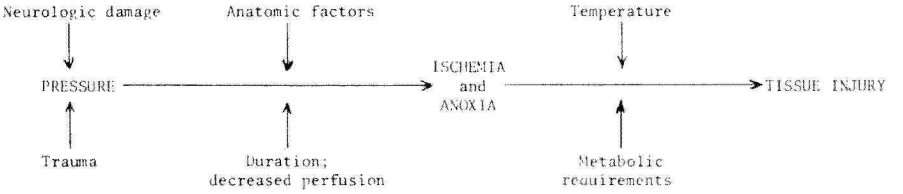

FIG. 11. Schematic diagram of the pathogenesis of pressure-induced lesions.

vessels as well as the development of clinically and histologically indistinguishable lesions in the numerous situations detailed above.

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