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STUDIES OF THERMAL INJURY
III. THE PATHOLOGY AND PATHOGENESIS OF CUTANEOUS BURNS
AN EXPERIMENTAL STUDY *

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In Study II of this series,[1] measurements of the reciprocal relationships of time and surface temperature with respect to the capacity of thermal exposures to destroy the epidermis of man and pig were reported. This report concerns the pathogenesis and pathologic characteristics of cutaneous burns in relation to the duration and intensity of thermal exposure and to their susceptibility to organization, repair, and healing.

SOURCE OF MATERIAL

The material used for pathologic study was derived from several sources as indicated in Table I. Many of the hot water burns of both human and porcine skin were made in Study II of this series to establish the reciprocal relationship of time, temperature, and epithelial destruction. The method of their production has been fully described. Since the majority of the lesions described in Study II were not excised until they had been under clinical observation for days or weeks, many duplicate exposures were made and excised in order to observe the sequence of microscopic changes that took place between the incurrence of various types of injury and their repair. To acquire this material, approximately 60 additional hot water exposures of pigs' skin were made and examined microscopically after recovery periods ranging from a few seconds to several weeks. Additional porcine material was derived from a series of burns made by exposure to hot air at temperatures varying between 80° and 900° C.[2]

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There were two series of human burns, one comprised of 33 experimentally produced lesions which were studied clinically but were not excised for microscopic examination, and the other of skin specimens obtained at post-mortem examination of victims of accidental conflagrations.

Sections of tissue for microscopic examination were cut from specimens that had been fixed in Zenker-formol or 4 per cent formaldehyde solution. Phloxine and methylene blue stains were made routinely

TABLE I

Sources and Kinds of Material Used for Study of the Pathogenesis of Cutaneous Burns

Subject	Source of heat	Range of exposure		Range of recovery period
		Temperature	Duration	
Pig	Water	44° to 100°C.	0.5 sec. to 7.5 hrs.	1 min. to 4 wks.
Pig	Air	80° to 900°C.	0.5 sec. to 45 min.	1 min. to 3 days
Man*	Water	44° to 60°C.	3 sec. to 6 hrs.	1 min. to 4 wks.
Man	Air	?	?	Less than 1 hr.

* Lesions not excised for microscopic study.

and were augmented by sections stained with hematoxylin and eosin or by Pollak's modification of Masson's trichrome method. Many sections were stained by the Feulgen technic.

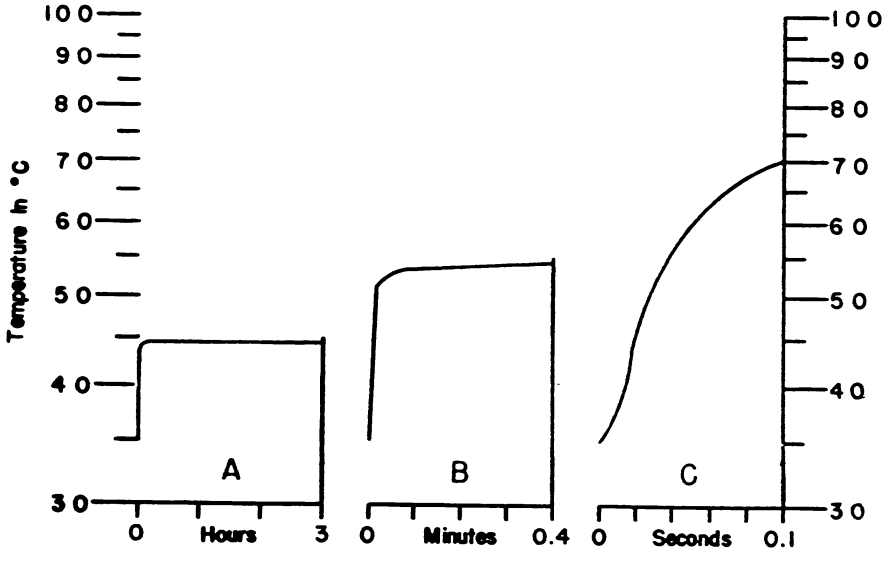
GENERAL CONSIDERATION OF THE QUANTITATIVE AND QUALITATIVE EFFECTS OF HEAT ON THE SKIN

A cutaneous injury caused by hyperthermia may be characterized quantitatively according to the depth to which the tissue has been destroyed, or qualitatively according to the nature of the changes that have occurred. The characterization in Tables II and III in Study II of hyperthermic episodes as sub-threshold, threshold, and supra-threshold refers to their quantitative capacities for injury production, the determining factor being whether the exposure in question is insufficient, just sufficient, or more than sufficient to cause transepidermal necrosis.

Thus, any exposure that failed to cause complete destruction of the epidermis was designated as sub-threshold and any reaction short of transepidermal necrosis was one of the first degree. A second degree reaction was one caused by the shortest exposure at any given temperature, or the lowest temperature at any given time that resulted in full-thickness destruction of the epidermis. Although it was not possible to destroy the entire thickness of the epidermis without some damage to the underlying connective tissue, dermal necrosis was a

relatively insignificant feature of a threshold exposure. A third degree reaction was one caused by an exposure that was supra-threshold in respect to time or temperature and was accordingly one in which a significant degree of dermal necrosis usually accompanied the destruction of the epidermis.

When account is taken of the potential variations in the intensity and duration of the different thermal exposures that are capable of producing burns of similar severity, it becomes apparent why thermal lesions may be qualitatively dissimilar even though their ultimate effect in terms of the amount of tissue destroyed is the same. This fact is more readily appreciated by reference to Text-Figures 1 and 2. The



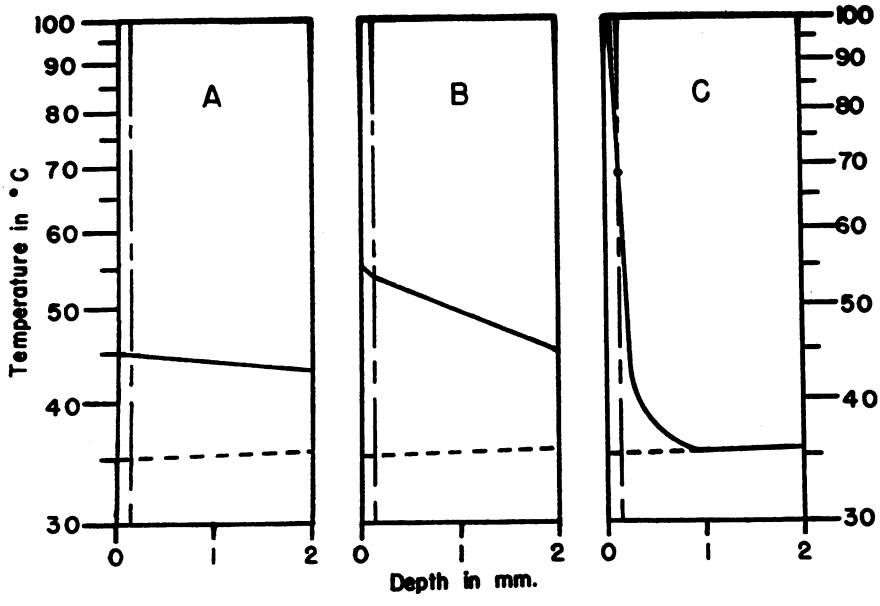
Text-Figure 1. Curves depicting the change in temperature that would occur at the interface between dermis and epidermis during surface exposures of 45° (A), 55° (B), and 100° C. (C). Each of these was a threshold exposure in that 3 hours, 0.4 minutes, and 0.1 second, respectively, are estimated to be the shortest time at the indicated temperature that would cause transepidermal necrosis. (Curves derived from data reported by Henriques and Moritz.[3])

critical temperature, so far as the ultimate fate of the epidermis is concerned, is that attained at the interface between epidermis and dermis rather than that of the surface. In Text-Figure 1 are shown the estimated changes * in temperature that would occur at the basal cell level during the course of thermal exposures at three different surface temperatures if each was terminated at a time calculated to be just adequate to destroy the epidermis. In Text-Figure 2 are shown the temperatures that would prevail at different depths below the sur-

* Calculations based on data presented in Study I of this series.[3]

face of each at the moment that the duration of the exposure was just sufficient to cause irreversible injury of the entire thickness of the epidermis.

In each instance, the effects would be quantitatively similar, in that irreversible cellular injury would extend to, but not far beyond, the basal cell layer. That qualitative differences in the resulting reactions might exist despite their quantitative similarity can be inferred from the fact that in the exposure shown in Text-Figure 1-A, the epidermis



Text-Figure 2. Curves depicting the temperature gradient through the skin that would exist at the conclusion of three types of thermal exposure at the termination of an exposure just sufficient to cause epidermal necrosis. The solid line traversing each chart from left to right depicts the temperature gradient from the surface to a depth of 2 mm. (dermis-fat interface). The transverse broken line depicts the pre-exposure gradient through the same thickness of skin. The vertical broken line indicates the approximate depth (circa 100 μ) of the dermis-epidermis interface. In A, the surface of the skin had been maintained at 45°C. for 3 hours. At the end of this time the temperature at a depth of 2 mm. had been raised from 36° to 44° C. In B, the surface of the skin had been maintained at a temperature of 55°C. for 0.4 minutes. At the end of this time the temperature at a depth of 2 mm. had been raised from 36° to 47°C. In C, the surface of the skin had been maintained at 100°C. for 0.1 second. At the end of this time there had been no change in the temperature at a depth of 2 mm. (Curves derived from data reported by Henriques and Moritz.[8])

was destroyed by a 3-hour episode of hyperthermia, the intensity of which at no time rose above 44.8° C. at the basal cell level. Approximately the same amount of irreversible change would be sustained as the result of the exposure depicted in 1-C. In the latter

instance, the epidermis would be destroyed in approximately 0.1 second by an episode of hyperthermia in which the temperature at the basal cell level rose sharply and briefly to 70° C. The exposure depicted in 1-B falls about midway between these extremes. Although the total amount of irreversible injury is about the same in each, it is to be expected that the three lesions produced by these exposures would differ qualitatively.

An additional reason for the occurrence of qualitative differences in quantitatively similar reactions to thermal exposures of different intensity is shown in Text-Figure 2, in which are depicted the calculated transcutaneous thermal gradients to a depth of 2 mm. that would exist at the moment of completion of the same three episodes of hyperthermia that are illustrated in Text-Figure 1. In each instance, irreversible thermal injury would extend to, but not appreciably beyond, the basal cell layer. In the exposure depicted in 2-A, the temperature of the dermis to a depth of about 2 mm. would be elevated above the normal level for at least 2 hours. In the exposure depicted in 2-C, the transcutaneous thermal gradient was so steep that the resulting temperature changes in the dermis were exceedingly brief and superficial. It is apparent why the epithelial cells would be destroyed in 2-C with relatively little disturbance of the dermis, whereas in 2-A the same or even a lesser degree of epidermal injury would be accompanied by a severe and persistent vascular disturbance.

First Degree Reactions

Hyperemia, Edema, and Cyanosis

Dilatation of the superficial vessels sufficient to cause visible reddening of the skin usually followed, and, in the case of exposures of low intensity, characteristically preceded the occurrence of recognizable damage to the epidermis. An exception to this generalization was the absence of vascular reaction in animals suffering circulatory failure. In such there was frequently a depression of vasomotor irritability so profound that injurious episodes of hyperthermia of either high or low intensity failed to elicit vascular reactions despite the occurrence of extensive epidermal injury. Another circumstance in which thermal damage of the epidermis was sustained with little or no vascular reaction was when an exposure to intense heat was so brief that, although the surface was burned, there was little or no rise in dermal temperature.

In the case of flash (circa 0.5 second) exposures to flame temperatures it was possible to carbonize superficial shreds of the stratum corneum without causing sufficient rise in sub-surface temperature to

damage the basal layer of epithelial cells or to cause a perceptible vascular reaction. The initial transepidermal thermal gradients established by such exposures were so sharp that the presence of a thin film of moisture on the surface of the skin was sufficient to make the difference between reaction and no reaction in the case of near-threshold exposures.

Attention has already been called to the fact that the duration of an episode of hyperthermia of low intensity must be greatly prolonged if it is to produce an injury quantitatively comparable to one resulting from an exposure of high intensity. Since the dermal blood vessels are far more responsive to temperature changes than are the epithelial cells, it can be understood why severe and persistent vascular reactions were often elicited by protracted episodes of hyperthermia of low intensity that failed to harm the epidermis (Text-Fig. 1).

There was considerably greater variation among human subjects than among pigs in respect to the vascular reactions to cutaneous hyperthermia. The variability of dermal vascular reactions in human subjects was so great and the number of reactions studied in this investigation so few that little could be inferred as to the extent to which animal data can be applied to man in this respect. The impression was gained that the thermal stimulus necessary to cause visible erythema in most human subjects was substantially lower than that required to elicit erythema in the pig. In man the change in skin color was usually more intense and of longer duration than after an identical exposure in the pig.

That an active circulation of blood was maintained through the dilated capillaries of an evanescently erythematous skin was indicated in part by the pink or red color of the surface and in part by the fact that the surface temperature * during such a reaction was characteristically between 0.5° and 1.5° C. higher than that of the adjacent skin.

An evanescent erythematous reaction to heat could not, as a rule, be recognized in sections prepared for microscopic examination. Vessels, the seat of physiologic dilatation, usually contracted during or immediately after excision, and it was difficult or impossible to distinguish a sample of physiologically hyperemic skin from one that was normal or even ischemic.

When cutaneous hyperthermia was prolonged to between 40 and 60 per cent of the minimum time required for the production of transepidermal necrosis in either man or pig, it characteristically resulted in a severe and pathologic vascular reaction with edema and cyanosis,

* Determined by means of the fine wire thermocouple described in Study VIII.[4]

and one which persisted for days rather than minutes or hours. That the flow of blood through the dilated capillaries was slowed was indicated by the blue or purple color of the surface in contrast to the pink or red color caused by the more evanescent active hyperemia. The surface temperature of such a lesion during the first few hours was frequently found to be from 0.5° to 2° C. below that of the adjacent normal skin. That the reaction was pathologic rather than physiologic was indicated also by the fact that in both man and pig it was almost invariably accompanied by cutaneous edema. Within the first hour after the onset of a vascular injury of this grade, the water content of the dermis was increased by as much as 100 per cent.

Microscopic examination of reactions of this type at varying periods after exposure in the pig confirmed the clinical observation in both pig and man that thermal exposures of relatively low intensity may result in severe and protracted disturbances of the dermal blood vessels without causing irreversible damage to the overlying epithelial cells. The capillary loops of the dermal papillae became dilated, elongated, and filled with closely packed masses of erythrocytes. Separation of collagen fibers by edema fluid was obvious and perivascular mantles of extravasated erythrocytes were often seen. The escape and extravascular deterioration of erythrocytes were often sufficient to result in brown discoloration of the target area for as long as 1 week, due to the formation of hemosiderin. Extravascular fibrin was not encountered nor did the collagen fibrils appear to be swollen. Between 12 and 24 hours after such an injury was sustained, occasional polymorphonuclear leukocytes were found in the edema fluid. Neither thrombosis nor visible alteration in the vascular endothelium was seen despite the fact that superficial vessels were filled by static, sausage-like agglomerates of red blood cells.

Reversible Impairment of Epidermal Anchorage

During most, and possibly all, injurious episodes of cutaneous hyperthermia in which the temperature of the epidermis was maintained for a sufficient time at 49° C. or higher, there was a brief interval subjacent to the threshold for transepidermal necrosis during which there was reversible impairment of the adhesion of epidermis to dermis.

The attainment of this degree of injury was recognized by the ease with which the epidermis could be dislodged by friction. If the exposure was discontinued before further injury was sustained and if the loosened epidermis was not dislodged by trauma or vesication, the change was potentially reversible in the case of the pig. After

12 or 18 hours the original firm anchorage of the epidermis was usually regained. Unless the exposure had been excessive, such injuries subsided without evidence of cell death.

When skin altered in this manner was protected against mechanical artifact, there was no microscopic evidence in either the epithelium or the underlying dermis by which impairment of the epidermal anchorage could be recognized. However, when sufficient friction was applied to the temporarily insecure porcine epidermis to cause its detachment, microscopic examination revealed a fringe of uprooted or fractured tonofibrils protruding from the lower ends of the detached basal epithelial cells. The protruding fibrils appeared to have been pulled out of their anchorage in the superficial dermal feltwork of collagen fibers. It was not determined whether the essential change responsible for such epidermal instability was a deterioration of the extracellular extensions of the tonofibrils, which predisposed them to rupture, or a softening of the dermal collagen in which they were embedded. The latter was considered the more plausible explanation of the phenomenon. In man it is doubtful that the tonofibrils of the epidermal cells have much if anything to do with the attachment of epidermis to dermis. In human skin, the epidermis appeared to be cemented to, rather than rooted in, the dermal collagen.

It has already been indicated that when porcine skin sustained this type of cutaneous burn, recovery sometimes took place within 24 hours without death of cells, providing the damaged area was protected against mechanical disturbance during that period when its anchorage to the dermis was insecure.

Too few appropriate specimens of human burns were available for microscopic examination to permit conclusions regarding the threshold at which, or the frequency with which, this particular type of first degree thermal injury occurs in man. The opinion was gained from clinical observations of human burns that thermal exposures insufficient to cause primary epidermal necrosis may result in a temporary impairment in the adhesion between epidermis and dermis. If such a temporarily insecure layer of epidermis is detached by friction or vesication, it will undoubtedly die if it remains dislodged. It is entirely possible that the phenomenon of vesication results, in some instances, in secondary destruction of human epithelial cells that would otherwise survive. If this be true, and if the thermal exposure has been insufficient to cause primary transepidermal necrosis, the immediate institution of pressure to prevent epidermal displacement by vesication should predispose to early and uncomplicated healing of what might otherwise become an open lesion.

Irreversible Thermal Injury of Epidermal Cells

Material for microscopic study was available from almost every conceivable kind, grade, and stage of thermal injury of the skin of the pig. Although a wide range of experimental thermal injuries of human skin was studied clinically, most of the burns that were available for microscopic examination were obtained from autopsies. Thus, there was no direct information regarding the intensity or duration of the thermal exposures that were responsible for the burns of human skin that were studied microscopically. The impression was gained however, that apart from the phenomenon of vesication, the cytologic changes induced by heat in the epidermis of man were similar, if not identical, to those observed in the pig (Figs. 1 to 6). Attention has already been directed to the fact that the time-temperature threshold for the destruction of epidermis is almost identical in human and porcine skin.

The first microscopic evidence of irreversible thermal injury of the epidermis consisted of what appeared to be a change in the distribution of water and solids within the nuclei of the cells of the intermediate zone. As the nuclei swelled, their chromatin granules coalesced to form compact crescentic masses immediately beneath and attached to one side of the nuclear membranes. When the swollen nucleus ruptured, the peripherally distributed chromatin contracted to form a dense and irregularly shaped central mass which remained separated from the surrounding cytoplasm by clear fluid. This fluid, whether extruded into the nuclear lacuna or contained within the distended nuclear membrane, was faintly basophilic and sometimes contained a few, fine, Feulgen-positive fragments of chromatin.

Pyknosis of nuclei was by no means pathognomonic of thermal injury. Spontaneous nuclear pyknosis was sometimes seen in the upper zone of unheated epidermis and was caused by injuries other than heat.

In the case of sub-threshold exposures sufficient to injure the upper layers of epidermal cells, but insufficient to cause transepidermal necrosis, the above-described types of nuclear change were frequently focal and difficult to distinguish from qualitatively similar changes in control material. Even though it could be plausibly assumed that all of the cells at a given level were exposed to the same degree of hyperthermia, it was not uncommon to find groups of cells with normal appearing nuclei interspersed among those with nuclei that showed advanced degenerative change (Fig. 2). The reason for this apparent difference in the susceptibility of cells in the same layer to heat was not apparent.

When the thermal exposure was of sufficient intensity or duration to cause irreversible cellular injury, nuclear changes of the kinds de-

scribed in the foregoing paragraphs were usually apparent immediately after the conclusion of the episode of hyperthermia. This was not invariably the case, however, and after certain exposures at relatively low temperature (under 47° C.) a post-exposure interval of between 6 and 12 hours was sometimes required for the development of recognizable nuclear alterations. Moreover, when the exposure was of sufficient severity to cause pseudovesication in the pig or true vesication in man, many of the nuclei which were apparently undamaged at the conclusion of the exposure disintegrated during the next 24 hours.

When the episode of hyperthermia was such as to cause visible alterations in nuclear structure, there was inhibition of mitotic division throughout the entire area of exposure for many hours. There was no evidence derived from the microscopic study of sub-threshold exposures to indicate that hyperthermia predisposed to acceleration of mitotic activity. The impression was gained that nuclear swelling with coalescence of chromatin granules constituted evidence of an irreversible cellular change and invariably led to premature death and desquamation of the altered cells.

In the pig, the irreversibly damaged epidermal cells were gradually desquamated over a period of 1 week to 10 days in the form of thin brown scales.

Alterations in the appearance of nuclei in the upper and intermediate layers of epithelium were thought to provide the earliest morphologic evidence of primary thermal injury of the epidermis and were frequently encountered without perceptible damage to the cells of the basal layer. Characteristically, the earliest change in the basal cell layer caused by hyperthermia was cytoplasmic rather than nuclear. The injured basal cells swelled and their cytoplasm became vacuolated and increasingly acidophilic. The vacuolization appeared to be due in part to imbibition of fluid and in part to redistribution of water and solids within the cells.

The fluid contained within the cytoplasmic vacuoles was clear, nonsudanophilic, and sometimes contained a delicate mesh of granular amphophilic débris. With severe injury there was widespread rupture and disintegration of the lower ends of the basal cells.

Second Degree Reactions

Transepidermal Necrosis

The time-temperature characteristics of exposures just sufficient to cause transepidermal necrosis in both man and pig are indicated in Text-Figure 4 of Study II. In man, it could usually be determined whether or not a thermal exposure had destroyed the epidermis by

the occurrence or nonoccurrence of vesication within the first 24 hours. To recognize with certainty during the first day or two after a near-threshold exposure whether or not porcine epidermis had been destroyed it was necessary to excise the skin and examine it microscopically. When the area of injury was 7 mm. in diameter and when the duration and intensity of the exposure was at or not far above the threshold required for transepidermal necrosis, the time usually required for complete healing was between 5 and 10 days in the pig and between 1 and 2 weeks in man.

In the pig, microscopic evidence that an exposure had been sufficient to cause transepidermal necrosis was provided by the changes that had occurred at the basal cell level. With the disintegration of the cytoplasm of the proximal or lower ends of the injured basal cells, there was at first, focal, and later, extensive, spontaneous detachment of the epidermis from the dermis. In the pig, the amount of fluid that collected beneath the loosened epidermis was never sufficient to produce true vesication.

With still more severe hyperthermia, the cytoplasmic disintegration of the basal cells was followed by nuclear changes similar to those seen in the more superficially located cells. When the epidermal detachment was incomplete, stretching and attenuation of the remaining bridging cells and their nuclei were often seen. Such attenuated masses of chromatin were often stretched to two or three times the original length of the entire cell.

In the event that the surface temperature of the epidermis was brought rapidly to a level of 55° C. or higher, and maintained at such a level long enough to produce a third degree burn, transepidermal coagulation usually masked any nuclear swelling that may have occurred. In such an event, neither the cytoplasm nor the nuclei of the epithelial cells appeared swollen (Fig. 7). On microscopic examination, both appeared shrunken, the former being intensely acidophilic and the latter small and homogenously basophilic.

Vesication

Attention has already been called to the fact that a common effect of heat on the skin of both man and pig is impairment of the attachment of the epidermis (Figs. 5 and 6) to the dermis, and the opinion was expressed that this may have been due either to a change in the physical state of the superficial dermal collagen or to disruption of the basal layer of epithelial cells. A common collateral effect of cutaneous hyperthermia, and one that was apparently essential to true vesication, was an outpouring of fluid from the dermal capillaries.

When a thermal exposure of human skin was sufficient to impair the attachment of the epidermis, the amount of edema fluid that collected between it and the dermis was usually sufficient to elevate and stretch the entire layer of dead, dying, and living cells to form a vesicle. Although vesication of human skin was usually an almost immediate response to a thermal exposure of sufficient severity to cause primary epidermal injury, there were several circumstances in which it was either delayed or inhibited.

Delayed vesication was most frequently seen after exposures of long duration at low temperatures or after flash exposures at high temperatures. In both circumstances it seemed likely that the delay was due to the fact that the vascular damage was relatively mild, and that hours rather than minutes were required for enough fluid to collect beneath the damaged epidermis to form a vesicle. Also vesication was delayed or prevented when the injury was so overwhelming that the dermis and its superficial capillaries were almost immediately coagulated. With such thermal injury, the level at which edema developed was too deep to result in vesication (Fig. 8). Thus, in man, the nonoccurrence of vesication after a thermal exposure sufficient to cause severe injury of the epidermis may mean that the dermal hyperthermia was either inadequate to result in edema or that it was so overwhelming that the superficial capillaries were almost immediately occluded.

In no instance was true vesication of porcine skin observed. This was true despite the fact that many of the injuries met a prerequisite to vesicle formation, namely, sufficient impairment of the adhesion between epidermis and dermis to permit easy mechanical detachment of the former (Fig. 5). Failure of the pig to vesicate appeared to be due to the fact that the amount of edema fluid that penetrated the surface of the dermis was never sufficient to elevate the epidermis. In the absence of evidence to the contrary, a tenable explanation for nonvesication in the pig was that an episode of hyperthermia that was sufficient to impair the attachment of the epidermis to the dermis characteristically altered either the superficial feltwork of dermal collagen fibers or the walls of the capillaries contained by it, in such a way that they became virtually impermeable to edema fluid.

The nature, or for that matter, the existence, of this theoretical alteration in the permeability of the collagen or the capillary walls was not disclosed by microscopic examination. When the severity of an exposure was considerably in excess of that required to destroy the epidermis, swelling of the superficial dermal collagen and occlusion of its capillaries could be recognized. There was a wide range of exposures between the threshold for epidermal necrosis and that for recognizable

swelling of collagen or occlusion of capillaries in which the microscopic examination of the pig's skin disclosed no explanation for failure of porcine skin to vesicate.

Third Degree Reactions

The more a thermal exposure exceeded the threshold required for destruction of the epidermis, either in respect to temperature or time, the deeper the injury and the longer the recovery period necessary for repair and regeneration. In both pig and man, several weeks represented the minimum healing time if a significant degree of dermal injury had been sustained.

Further Changes in the Epidermis

In the case of the pig, prolonged exposure at a relatively low surface temperature (under 55° C.) caused relatively little additional change in the microscopic appearance of the epidermis. In the higher range of surface temperatures, a significant prolongation of the rate of duration of exposure beyond the time necessary to destroy the epidermis modified the quality of the superficial changes both in human and porcine skin. In man, vesication was permanently inhibited and in both man and pig the loosened epidermis became reattached to the damaged dermis (Figs. 7 and 8). Early shrinkage of both the cytoplasm and the nuclei of the damaged cells occurred before there was opportunity for the development of the retrogressive changes observed in first and second degree reactions. The higher the temperature, the shorter the time required to cause transepidermal coagulation. With exposures to superheated air, desiccation was superimposed on the effects of heat, and soon after the temperature rose above 300° C.. carbonization of the dry tissue began to take place.

Red and Pale Burns

The surface color of third degree burns ranged from pale gray through red, purple, and brown to black, depending on certain attributes of the exposures responsible for their production.

A black or carbonized surface resulted from exposures at temperatures in excess of 300° C. (Fig. 9). The precise temperature at which carbonization began was not determined.

A red, purple, or brown surface, due to the presence of blood in the superficial layer of the skin, resulted from exposures in which the dermal temperature was raised slowly enough to permit advanced engorgement of the superficial capillary plexus before the occurrence of coagulation.

A gray or ischemic surface indicated that the upper portion of the dermis had undergone thermal coagulation before the superficial capillaries had become fully engorged.

The reciprocal relationships of time and temperature as they relate to the visibility of hemoglobin beneath the surface of a third degree thermal reaction are shown in Table II of Study II. It was found that at atmospheric pressure and at surface temperatures of 65° C. or lower, burns appeared superficially hyperemic regardless of the duration of exposure. When a 70° C. surface exposure was interrupted at the end of 2 seconds, the lesion remained red, but if it were prolonged

TABLE II

Increase in Hemoglobin Iron in Skin and Subcutaneous Tissue following Thermal Injury

Condition of skin	Weight of iron per sq. cm. of sample	Estimated weight of blood per sq. cm. of sample
	(μg.)	(mg.)
Normal	2.4	5.5
	4.0	9.0
Moderate hyperemia	5.6	13
	12	26
Severe hyperemia	22	50
	24	55
	16	35
	16	35
	15	34

to 3 minutes, the zone of reactive hyperemia became overlaid by so thick a layer of coagulated tissue that it was no longer visible. Above 70° C. all exposures of 1 second or longer coagulated the superficial plexus of dermal capillaries so rapidly that most or all of the blood contained in them was displaced to a level too deep to be seen from the surface.

POOLING OF BLOOD IN HYPEREMIC BURNS

A qualitative impression of the pooling of blood in the dilated cutaneous vessels after an injurious episode of hyperthermia was derived from the photomicrographs shown in Text-Figure 2 of Study II. In order to learn something of the actual amount of blood that was present in such lesions, samples of both normal and hyperemic skin were excised for chemical examination. Samples of skin and subcutaneous tissue having an area of 25 sq. cm. and extending to the deep fascia were taken from the lateral thoracic area of each of 9 pigs and their iron content was determined.[5] Two of the samples represented normal skin and the other 7 were from areas of hyperemic burning.

It is apparent from the results of the experiments shown in Table II that a relatively large proportion of the total circulating blood of an animal may be pooled in the skin and subcutaneous tissue as a result of thermal injury. Calculations based on the amount of recoverable iron per unit of surface area of burned skin in relation to the body weight indicated that as much as 30 per cent of the erythrocytes of an animal suffering from generalized cutaneous hyperemia could be accounted for in the skin and subcutaneous fat.

THE EFFECT OF COMPRESSIVE HYPERTHERMIA ON THE COLOR OF A BURN

In Study II, attention has been called to the fact that pressure on the skin surface during exposure to heat does not increase the vulnerability of the epidermis to thermal injury except as it may improve the contact between a hot solid and the skin surface. It was found, however, that compression of the skin was capable of modifying the superficial color of the burn even though there was no increase in the severity of the lesion. To determine the circumstances in which compression of the skin during an episode of hyperthermia may modify the color of the burn, the experiments on pigs summarized in Table III

TABLE III

The Effect of Pressure upon the External Appearance of Burns

Temperature of surface	Duration of hyperthermia	Pressure on skin	External appearance of burn 24 hours after exposure	
			Ischemic	Hyperemic
(°C.)	(*seconds*)	(mm. Hg)		
70	5	0		+
	5	120	+	
65	30	0		+
	30	120		+
	60	120	+	
	1200	0		+
60	60	0		+
	60	120		+
	120	120	+	
	300	0		+
55	1800	0		+
	1800	120		+

were undertaken. In some, hot water was applied at atmospheric pressure, and in others it was applied with a compressive force of 120 mm. of Hg.

The results of these exposures indicated that the color of burns resulting from surface temperatures lower than 55° C. was not affected by pressure, but that an increase in pressure during exposures at

surface temperatures of 60° C. or higher determined whether the surface of the resulting burn would be ischemic or hyperemic. Thus, an exposure at atmospheric pressure at 60° C. produced a red burn even though it was extended for as long as 5 minutes. With increase in pressure, a 2-minute exposure at the same temperature resulted in a pale burn and yet the depth to which the tissue had been destroyed in the latter was less than that to which it had been destroyed in the former. At 70° C., a 5-second exposure at atmospheric pressure resulted in a red burn, but with an additional pressure of 120 mm. of Hg the resulting burn appeared ischemic.

Microscopic examination of these lesions provided evidence that the color of a burn was not a reliable criterion by which to judge its depth. After hyperthermic episodes of comparable duration and at the same surface pressure, a red surface color usually indicated that the lesion was less severe than one having a gray surface. Without knowledge of time, temperature, or surface pressure during the period of exposure, it is not possible to estimate the relative severity of burns on a basis of surface color.

OTHER EFFECTS OF HEAT ON THE DERMIS

After edema and pericapillary extravasation of erythrocytes, the earliest recognizable extravascular alteration of the dermis was swelling of collagen fibers. This occurred first in the most superficial layer where, in the case of porcine skin, the projecting tonofibrils of the basal epithelial cells were imbedded in the collagen of the subjacent connective tissue.

As the intensity and duration of the hyperthermia increased, the corium tended to lose its fibrillar character and became a thin lamella of homogeneous acidophilic material as though the individual fibers had been converted to a gel. With increasing exposure the swelling of collagen became apparent at greater and greater depths in the underlying connective tissue (Fig. 8). Expansion of collagen bundles tended to collapse and obliterate the loose perivascular areolar tissue. Contracted blood vessels appeared thick-walled and empty. Visible edema receded in advance of this type of alteration as though the fluid were imbibed or displaced by the denatured collagen. Not until 24 or 48 hours had elapsed was it possible by microscopic examination to recognize the line of demarcation between reversible and irreversible dermal injury.

From the intact blood vessels of the deeper and relatively uninjured tissues leukocytes migrated upward through the perivascular interstices and into the zone of denatured collagen. A frontier was eventu-

ally established between the tissue capable of recovery and that destined to be sequestered in the form of a desiccated crust. The deeper the lesion the longer the time required for the stabilization of such a frontier. The transition between the obviously necrotic tissue of the upper dermis and the least disturbed tissue of the deepest portion of the zone of hyperthermia was a gradual one.

Exudation of leukocytes occurred within a few hours, and within 24 hours usually served to delineate the zone within which the plane of irreversible injury would eventually become stabilized. Within 2 or 3 days, fibroblasts and new capillaries began to push up toward the surface in the interfascicular interstices of the denatured collagen (Fig. 10). The least affected connective tissue at the base of the reaction zone recovered quickly and without apparent loss of fixed tissue cells. The fate of the more severely injured collagen varied according to the extent to which it had been denatured. Thermal denaturation of collagen at temperature levels under 55° C. (Fig. 11) did not appear to result in the kind of coagulative change that made the collagen resistant to subsequent autolysis and organization. Collagenous denaturation at temperatures over 55° C. often resulted in an irreversible type of coagulation which resisted lysis and eventually led to sequestration en masse. Thus, deep and severe burns resulting from surface exposures lower than 55° C. were likely to remain soft and red and the necrotic tissue was susceptible to organization. Deep burns resulting from higher temperatures were characteristically firm and pale and there was sequestration but not organization of the necrotic tissue. Between these two extremes the dead and damaged connective tissue was infiltrated by leukocytes and penetrated by granulation tissue, and its necrotic elements were gradually resorbed and replaced by new connective tissue.

During the time required to establish the level of irreversible injury, tentative tongue-like masses of new epithelial cells grew out from the margins of the lesion and from the viable roots of partially destroyed hair follicles as though they were seeking a sufficiently well stabilized layer of connective tissue to provide support and nutrition. Repeated crops of such new epithelial cells extended over or into the granulation tissue and failed to survive, for reasons not disclosed by microscopic examination.

Summary

The transfer of heat to the skin at a rate sufficiently great to raise the sub-surface temperature to an appreciably higher level than that which is normal for the organism leads to a series of local reactive and alterative changes, the severity of which bears a direct relationship

to the degree and duration of the temperature rise. The nature of the change that occurs at any given depth below the surface of the exposed skin is determined in part by the intensity and duration of the temperature rise at that level and in part by the nature of the affected tissue.

The mildest form of epidermal injury produced by hyperthermia is latent in the sense that it is not associated with recognizable alteration in cell structure. Such injuries are reversible and the time required for their reversal increases in direct relation to the time required for their production.

The earliest visible evidence of thermal injury of the epidermis is a redistribution of chromatin within, and swelling of, the nuclei, first in the intermediate and later in the deepest layer of epithelial cells. Further injury results in swelling and disintegration of the cytoplasm of the basal cells and pyknosis of nuclei throughout the entire thickness of the epidermis. As the result of alterations in the basal cells or in the cement substance that binds them to the dermis, hyperthermia may result first in a reversible and subsequently in an irreversible impairment of the attachment between epidermis and dermis. If the temperature rise within the epidermis does not exceed a level of approximately 55° C., further primary thermal alterations of the epithelial cells either do not occur or are so slow in development as to be of negligible significance.

When the exposure is such as to result in a progressive rise in sub-surface temperature, the next step in the succession of alterative changes is the occurrence of transepidermal coagulation. When the epidermal temperature is raised rapidly to a level higher than 55° C., coagulative changes may mask both nuclear swelling and cytoplasmic disintegration. Further increases in the temperature of the epidermis result in progressive desiccation and eventually in carbonization.

The earliest visible alterative change in the dermis in response to hyperthermia is constriction of the superficial blood vessels. Ordinarily, this is followed almost immediately by vasodilatation. When the rise in dermal temperature is sufficiently rapid and high, the superficial vessels become permanently fixed in their initial reactive state of constriction and vasodilatation occurs only at deeper levels where the temperature rise has been less extreme.

Thermal vasodilatation characteristically leads to increased vascular permeability and edema formation. The escape of edema fluid at any particular sub-surface level requires, first, that the vascular injury at that level has been sufficiently severe to result in increased mural

permeability and, second, that it has not resulted in cessation of blood flow through the damaged vessels.

Although thermal exposures of appropriate intensity and duration impair the attachment of epidermis to dermis and increase the permeability of the superficial capillary plexus of the dermis in both pig and man, it is only in the latter that a sufficient amount of edema fluid collects beneath the epidermis to cause true vesication.

Absence of vesication in human skin that has been exposed to heat may indicate that the rise in dermal temperature was insufficient to cause increased vascular permeability, that insufficient time has elapsed for the collection of enough fluid beneath the epidermis to cause appreciable elevation, that the hyperthermia was so extreme as to have caused cessation in blood flow through the superficial capillaries, or that cutaneous ischemia and loss of vasomotor irritability were antecedent to the exposure to excessive heat.

As in the case of the epidermis, coagulative changes occur in the dermis when its temperature is raised to, and maintained for a sufficient period at, a level higher than 55° C. Further increases in dermal temperature may result in desiccation and carbonization.

It was found that the superficial appearance of a burn is not a reliable criterion by which to judge the depth to which the tissue may have been irreversibly injured. The surface of a relatively shallow burn may show coagulation and even carbonization if the exposure has been intense and brief, whereas a thermal exposure of insufficient intensity to coagulate even the most superficial portions of the skin may, nevertheless, cause deep destruction if sufficiently prolonged.

Although the quantitative results of a short exposure of high intensity may be similar to those of a long exposure at low intensity, there are likely to be significant qualitative differences between such injuries. Hyperthermia of high intensity results in a coagulative type of necrosis in which the dead tissue does not undergo autolysis, resists organization, and is usually disposed of by sequestration. Hyperthermia of low intensity results in a noncoagulative type of necrosis in which the dead tissue undergoes autolysis and is readily susceptible to organization.

Biopsy of a burned area within 24 hours should provide useful information pertaining to the depth and nature of injury. Recognition by microscopic examination of dermal coagulation would indicate eventual sequestration of the tissue so affected. Recognition of a zone of irreversible injury would indicate the need for debridement before attempting to graft new epidermis on the surface.

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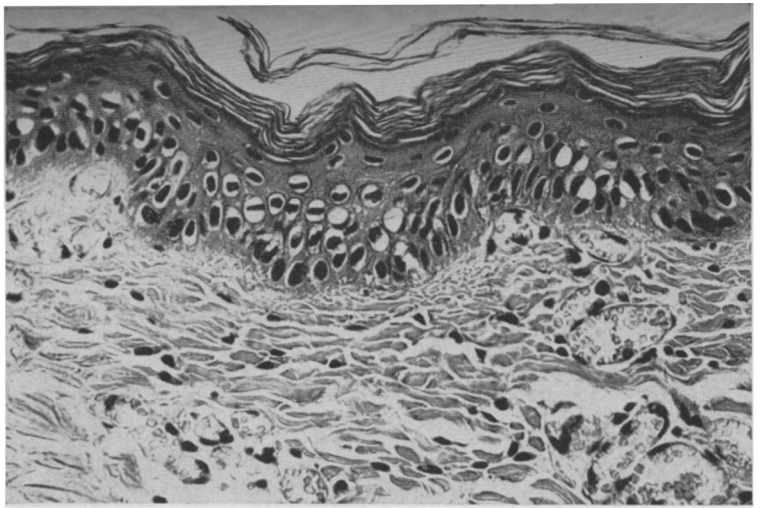
DESCRIPTION OF PLATES

PLATE 136

FIGS. 1 and 2. Photomicrographs of severe first degree burns of porcine (Fig. 1) and human (Fig. 2) skin showing the degenerative changes in epidermis. In Figure 1 there is generalized pyknosis of nuclei, and none of the epidermal cells included in the picture would have recovered. In Figure 2 the changes are focal rather than general and most of the altered nuclei are swollen and show peripheral displacement of the chromatin. This type of nuclear change precedes that shown in Figure 1. Both specimens were excised within 1 hour after the injury was sustained. In both instances the epidermal attachment to the dermis was insecure and the lesion shown in Figure 2 probably would have gone on to vesication in the normal course of events. × 400.

FIGS. 3 and 4. Photomicrographs of early second degree burns of porcine (Fig. 3) and human (Fig. 4) skin showing early spontaneous detachment of the epidermis from the dermis. Vacuolar cytoplasmic disintegration of the basal cell layer has been added to nuclear changes similar to those shown in Figures 1 and 2. In Figure 3 the tonofibrils that were uprooted from their anchorage in the dermis can be seen projecting from the detached basal cells. × 400.



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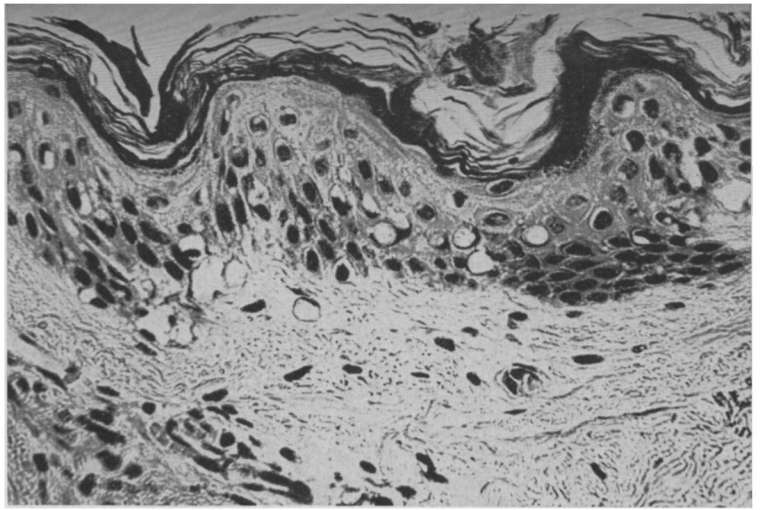

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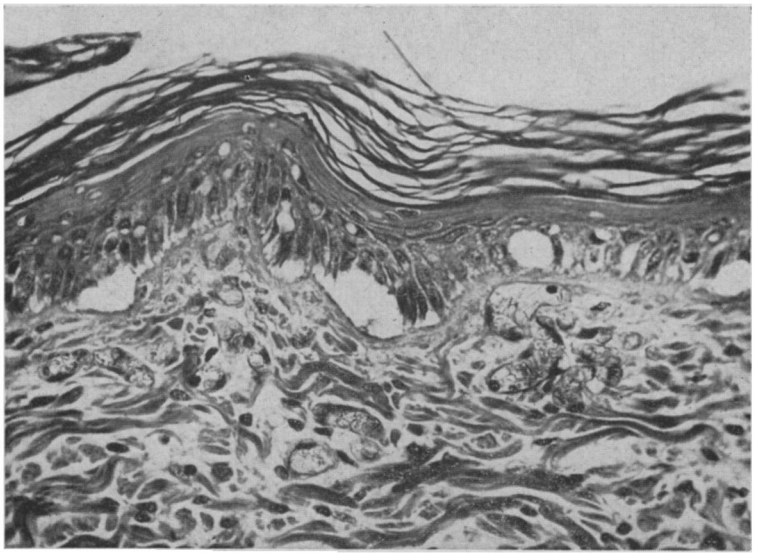

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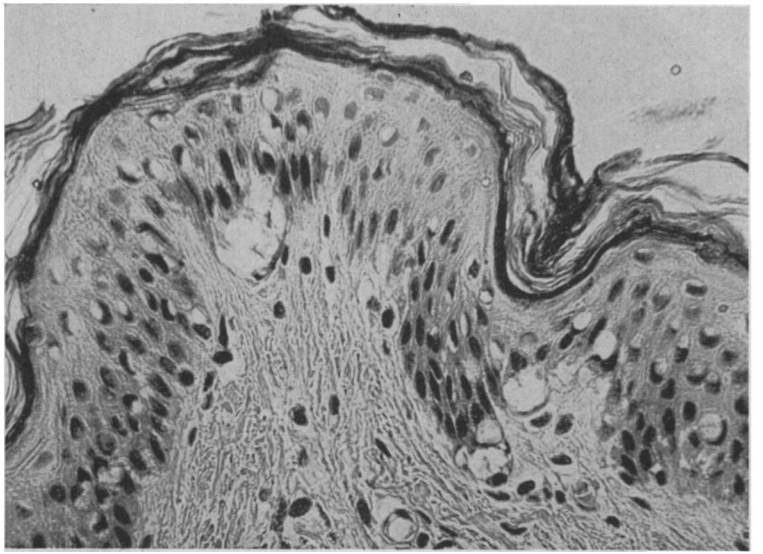

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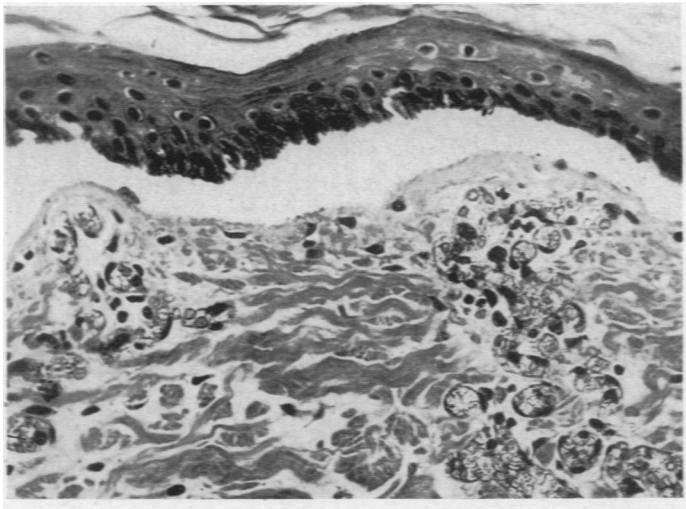
PLATE 137

FIGS. 5 and 6. Photomicrographs of a pseudovesicle of porcine skin (Fig. 5) and an early true vesicle of human skin (Fig. 6). In each, transepidermal necrosis is complete. In the case of porcine skin the detached epidermis would have remained *in situ* as a flaccid membrane. In the case of human skin the detached epidermis would have been elevated by the collection of edema fluid between it and the dermis. × 400.

FIG. 7. Third degree thermal injury of porcine skin showing coagulation of epidermis and dermis 24 hours after injury. Burn produced by maintaining surface of skin at 65° C. for 2 minutes. The bundles of denatured dermal collagen appeared swollen and homogeneous, and had become increasingly basophilic. Thermal reactions of this type were encountered only when the surface temperature had been brought to, and maintained at, a level of 55° C. or higher. Coagulative changes of this type render the necrotic tissue resistant to lysis and organization. × 400.



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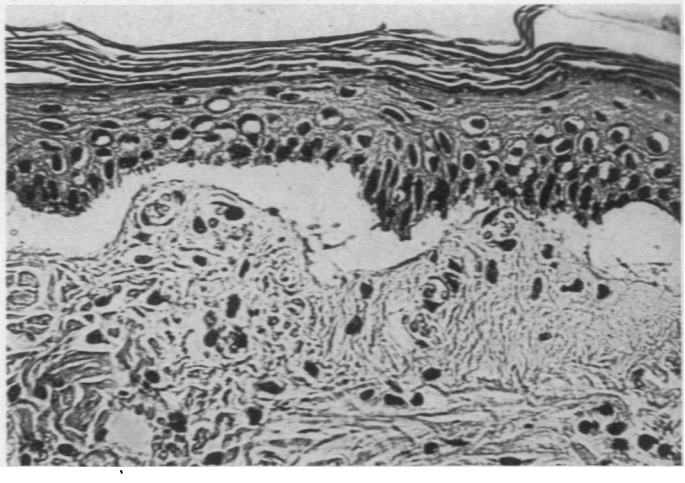

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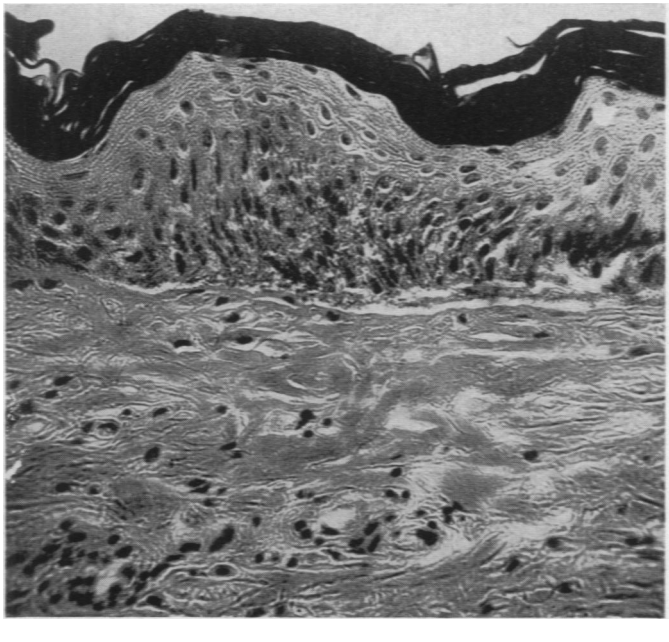

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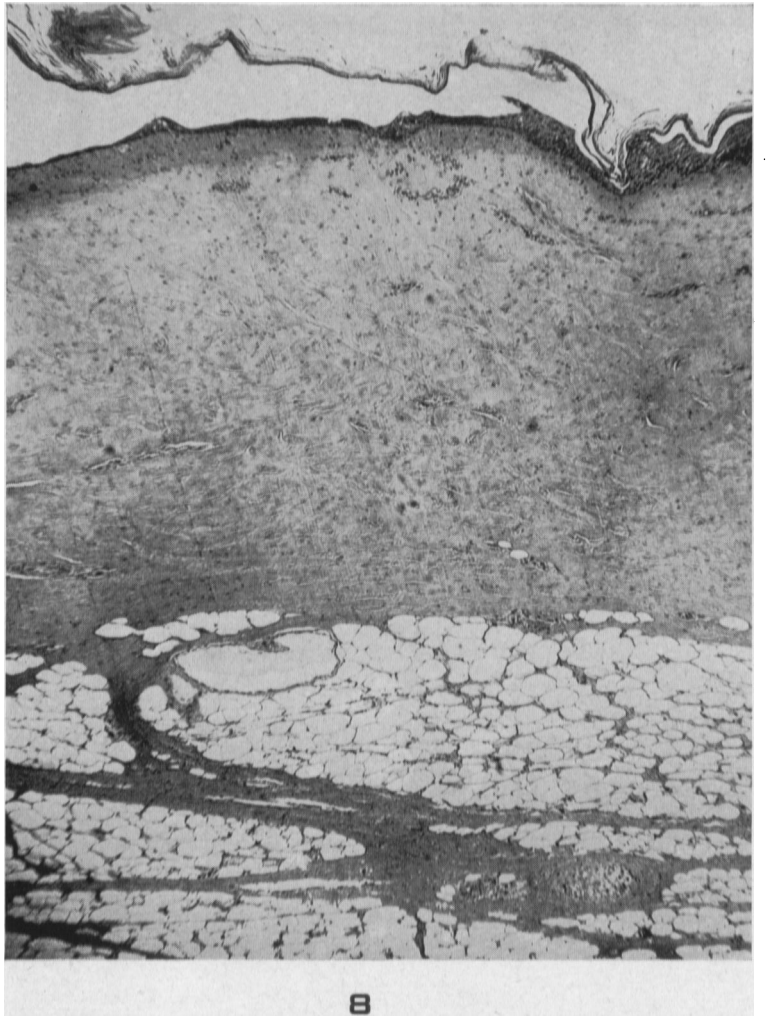
PLATE 138

FIG. 8. Transcutaneous coagulation resulting in a deep ischemic lesion, caused by a 5-minute exposure to circumambient (air) temperature of 200° C. × 85.

FIG. 9. Carbonization of surface of skin with desiccation and intense basophilia of coagulated dermis, caused by an exposure of 2.5 minutes to a circumambient (air) temperature in excess of 400° C. × 85.



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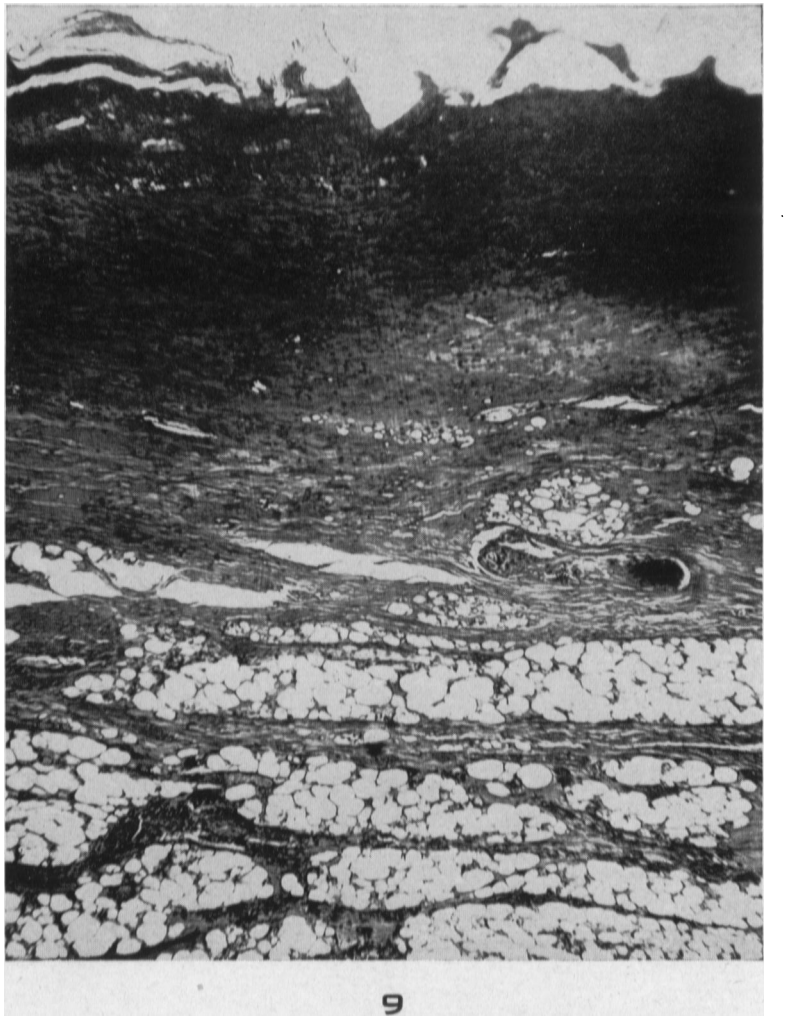
Moritz



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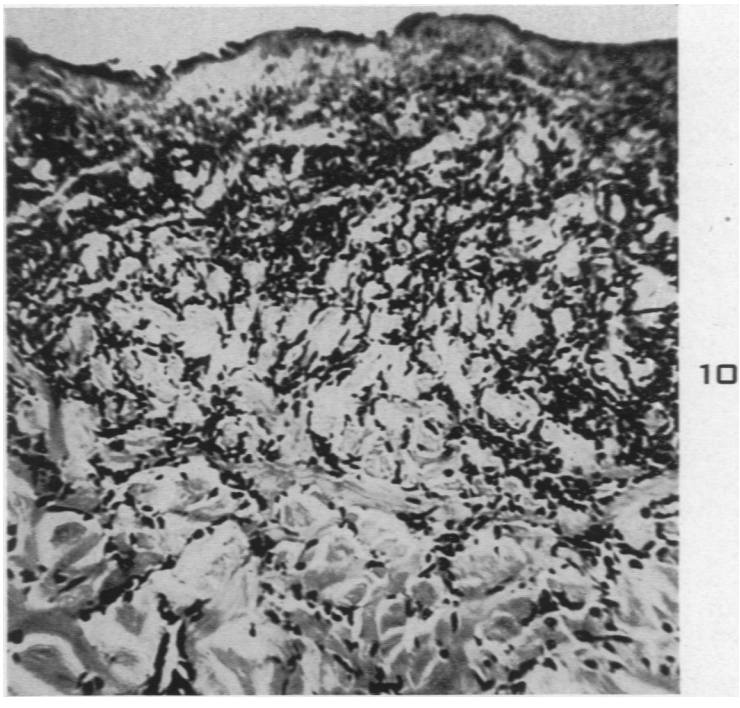
Thermal Injury

PLATE 139

FIG. 10. Photomicrograph of a third degree thermal reaction in porcine skin 72 hours after injury. Exudative cells have migrated into the interstices between the bundles of coagulated collagen. The precise level at which this injury will be stabilized is not yet apparent. Healing will be slow because of the resistance of the denatured collagen to autolysis and organization. × 400.

FIG. 11. A 24-hour-old third degree burn of porcine skin in which the necrotic dermal tissue was not coagulated, was already densely infiltrated by exudative cells, and was readily susceptible to organization and repair. Burn produced by maintaining the surface of the skin at 53° C. for 5 minutes; for comparison with burn shown in Figure 7 in which coagulation of dermal collagen had rendered it resistant to lysis and organization. × 400.



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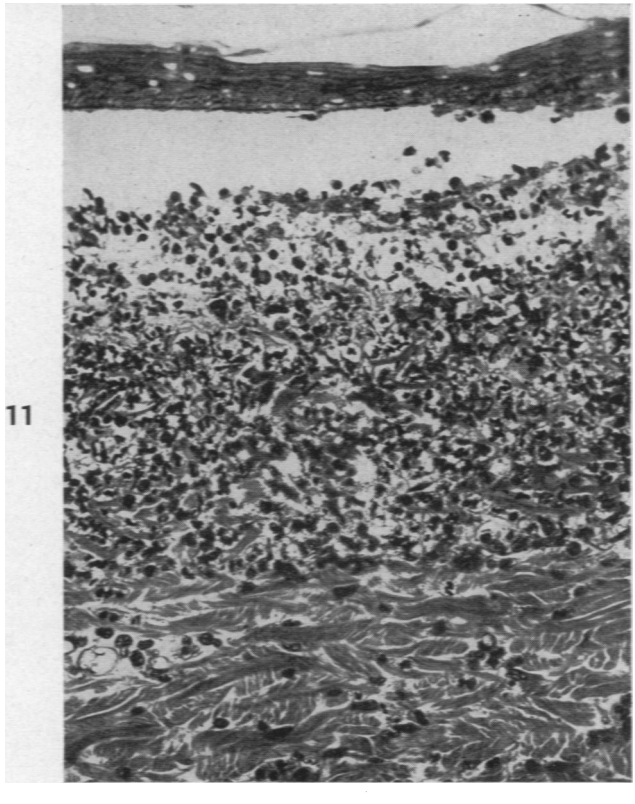

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Moritz Thermal Injury