STUDIES OF THERMAL INJURY

II. The Relative Importance of Time and Surface Temperature in the Causation of Cutaneous Burns *

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Although it is common knowledge that there is an inverse relationship between the intensity of a thermal exposure and the amount of time required to produce a burn, there is remarkably little available information as to the rate at which burning of human skin occurs at any given surface temperature or as to the pathogenesis and pathological characteristics of burns in which the duration and degree of rise in intracutaneous temperature was known or could be calculated with any degree of accuracy.

Considerable information regarding the time-temperature thresholds at which cutaneous burning occurs in animals is provided by the experiments of Hudack and McMaster [1] and of Leach, Peters, and Rossiter.[2] In the former, water at temperatures ranging between 42° and 67°C. either was applied directly or was passed through a thin-walled glass chamber, the base of which was brought in contact with the skin of mice. In the experiments performed by Leach, Peters, and Rossiter water was pumped through a metal chamber at temperatures ranging between 45° and 80°C. and the base of the chamber was held in contact with the skin of guinea-pigs for varying periods of time. Both groups of investigators observed that the time required to produce injury diminished rapidly as the temperature of the water was raised. The former reported that a source temperature of 44°C. was critical for the causation of hyperthermic edema. The latter reported that the critical temperature for causing permanent and irreversible injury of guinea-pig skin lies between 50° and 55°C. Neither of the above-cited investigations provided data from which the time-temperature requirements for the production of burns of human skin could be estimated.

Although Leach, Peters, and Rossiter [2] made a careful study of the pathological characteristics of different kinds of burns of guinea-pig skin, the extent to which these changes are representative of those that occur in cutaneous burning in man was not disclosed.

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The primary purpose of this investigation was to obtain information regarding the effects on human skin of episodes of hyperthermia of varying duration and of varying degrees of intensity. The direct approach would have been to make all experiments on human subjects. For various reasons this was not feasible. It was decided first to establish the time-temperature thresholds for varying degrees of cutaneous injury by experiments on an animal having a skin similar to that of man, and then by means of a relatively small number of critical exposures of human skin to establish the extent to which the more comprehensive animal data are applicable to man.

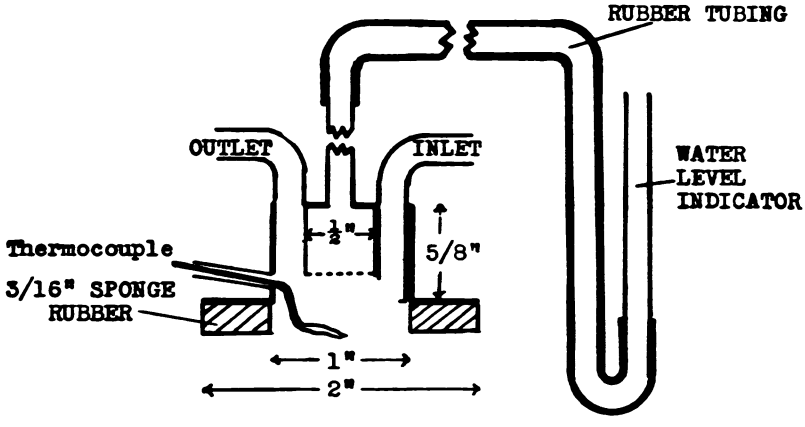
Method of Maintaining Surface of Skin at a Known Degree of Hyperthermia

The method employed by Leach, Peters, and Rossiter [2] for the production of burns in guinea-pigs was investigated and found to be unsuited to the purposes of this study. It was discovered that the temperature of the stream of hot water flowing through the upper and midportions of the metal chamber was significantly and variably higher than that of the surface of the underlying skin. As the water flowed from inlet to outlet there remained a relatively static layer of fluid at the bottom of the chamber. Thus, there were interposed two hindrances to the conduction of heat between the site of measured temperature and the surface of the epidermis, one being the metallic base of the chamber and the other being the layer of quiet fluid above it. Thermocouple measurements of the temperature of the underlying skin disclosed it to be as much as 1° lower than that of the stream of water at the level of the thermometer. In consideration of the fact that the rate at which burning occurs is almost doubled for each degree rise in temperature between 44° and 51°C., the desirability of employing a more precise method of controlling the temperature of the skin is obvious. Another reason for rejecting the method used by Leach, Peters, and Rossiter for the production of burns was that the skin was compressed by the metallic base of the chamber during the period of heat transfer. It was our desire to investigate the effects of hyperthermia independently of any physiological artefact that might be introduced by compressive occlusion of dermal capillaries during the period of exposure.

Direct exposure of the surface of the skin to a rapidly flowing stream of hot liquid was chosen as the method best adapted for the acquisition of these data. With this type of exposure, the surface of the skin could be maintained at the temperature desired without the establishment of an appreciable gradient (<0.1°C.) between it and the source of heat. There was no insulation of the surface by a static

layer of gas, liquid or solid, no heat loss through vaporization of surface moisture, and no diminution of sub-surface heat conduction due to vascular occlusion by the application of pressure on the surface. The method was simple to operate and led to remarkably reproducible cutaneous effects.

The applicator by which a running stream of hot water was brought in direct contact with the skin consisted of a metal cup, the brim of which was covered with a pad of closed-cell sponge rubber to insure a watertight contact. By means of an electric pump, water was circulated from a large constant temperature reservoir through the cup, the open end of which was applied to the skin. The rate of flow was regulated by a screw clamp on the inlet tube and by the height of the outlet tube (Text-Fig. 1).



Text-Figure 1. An apparatus for exposing the skin to a flowing stream of liquid. The surface is brought immediately to, and maintained at, a predetermined and constant temperature without altering surface pressure. The apparatus consists of a brass cup, the base of which is open to permit direct contact between heat source and skin. Water (or oil) was heated by a manually operated steam coil in a large reservoir and pumped through the cup. The pressure within the cup was regulated by adjusting the rate of flow and the level of the outlet.

Tangential flow of a liquid produces no vertical component of force and thus no vertical pressure. Vertical water pressure within the cup could be varied between 70 and 86 cm. of mercury by suitable adjustments of the aperture of the inlet and the height of the outlet tubes. A copper-constantan thermocouple measured the temperature of the water flowing next to the skin. During any period of exposure the temperature of the water flowing over the skin could be controlled to within 0.1°C.

Two methods were used to equilibrate the apparatus before applying it to the skin. In one, the apparatus was applied to a block of linoleum, adjusted to the desired pressure, and transferred to the skin site to be exposed as soon as the temperature equilibrium was reached. In the

other, the applicator was allowed to remain immersed in the hot water reservoir with the pump turned on until thermal equilibrium was established. The cup was then transferred immediately to the skin and adjusted to the desired water pressure.

Provision was made in the construction of this apparatus for studying the relation of the size of the area of exposure to the intensity of the resultant injury. This was accomplished by making the brim of the cup removable so that the area of skin to be exposed could be varied according to the aperture selected for use. Thus, in the same region on the same animal and under identical conditions of time, temperature, and pressure, circular targets having a diameter of either 7 or 25 mm. could be exposed.

Individual burns in the animal experiments were 25 mm. in diameter. This was larger than was desirable for human subjects and the diameter of the aperture of the cup was accordingly reduced to 7 mm. for the human experiments. Before doing so, however, it was established by animal experimentation that the reduction in the size of the exposure area did not make an appreciable difference in the effect on the epidermis.

Water was employed as the source of heat in all of the experiments summarized in Table II. Because the question was raised whether a hypotonic fluid such as water might modify the effects of heat, a series of comparable exposures were made in which oil was substituted for water. There was no appreciable difference between the injury-producing potentiality of rapidly flowing streams of water and of oil on either animal or human skin so long as the temperature and duration of exposure were the same.

Experiments on Pigs

The pig was used in these studies because it was found that no other readily available animal has skin that bears so close an anatomical resemblance to that of man.

Porcine Epidermis

The epidermis over the lateral body area of the pig measures approximately 0.1 mm. in thickness. Like that of man there are irregularities in the contour of both the upper and lower surfaces of the epidermis, those on the upper being due to an intricate system of intercommunicating linear depressions and those on the lower corresponding to the dermal papillae over which the epidermis is moulded (Fig. 1 in Study III *).[3]

* Studies of Thermal Injury, III, will appear in the November issue of The Journal.

Like that of man, the outermost zone or stratum corneum of the pig's epidermis consists of several loosely connected layers of desiccated and intensely basophilic remains of keratinized epithelial cells.

The second or granular layer is thin and consists of several layers of dead or dying squamous cells, the acidophilic cytoplasm of which contains many fine, deeply basophilic keratohyaline granules. Many of these cells have lost their nuclei. Others contain shrunken hyperchromatic nuclei or Feulgen-negative nuclear ghosts.

The third zone is comprised of several layers of aging squamous cells which no longer have any direct cytoplasmic attachment to the dermis. The cytoplasm is dense, deeply acidophilic, and appears desiccated. The cells are so closely packed that neither intercellular bridges nor spaces can be recognized. Many of the nuclei are relatively small and more densely packed with chromatin granules than those of the deeper cells.

The fourth zone consists of cells in transition between the squamous and the basal cell layer. The transitional cells are large and polyhedral and many of them still have an attenuated foot-like cytoplasmic attachment to the dermis. It is in this zone that intercellular bridges of tonofibrils are most readily visualized. The cytoplasm is moderately basophilic. The cell outlines are distinct and the intercellular spaces are clearly defined. The nuclei are larger and rounder than those of the more superficial cells and contain several coarse and many fine granules of chromatin.

The fifth zone is comprised of the basal cells which, save for their cuboidal or columnar shape and their palisade-like arrangement on the dermis, are essentially similar to the overlying transitional cells. Projecting from the inferior surface of the basal epidermal cells of the pig are many robust tonofibrils which appear to be embedded in the dense feltwork of fine collagen fibrils that comprise the superficial zone of dermis. No such fibrillar anchorage of epidermis to dermis can be seen in human skin (Figs 1 to 6 in Study III).[3]

The microscopic appearance of the epidermis of both man and pig suggests that there is a progressive loss of intracellular water as the epithelial cells grow older and move away from the dermis. The nearer the surface the more desiccated the cells appear. The entire stratum corneum and most of the cells of the granular layer appear to be incapable of vital reaction.

Porcine Dermis

The dermis covering the lateral body surface of immature pigs measures between 1.0 and 2.0 mm. in thickness and is generally more compact than that of man. In both pig and man the superficial portion

of the dermis comprising the papillary layer or corium is characteristically a soft, thin, loosely arranged feltwork of delicate collagen fibrils in which there appears to be an abundant amount of interstitial fluid. In man it is readily distinguishable from the thick underlying reticular layer which is comprised of robust and closely interwoven bundles of collagen fibrils. Elastic fibrils are more numerous in human than in porcine skin. On the lateral body surface of the pig the corium tends to be thinner and less well defined than it is in man and in places is only slightly less compact than the reticular zone (Figs. 1 to 6 in Study III).[3] The deeper portion of the reticular connective tissue sends trabecular extensions into the underlying adipose hypodermis.

Blood Vessels of Porcine Skin

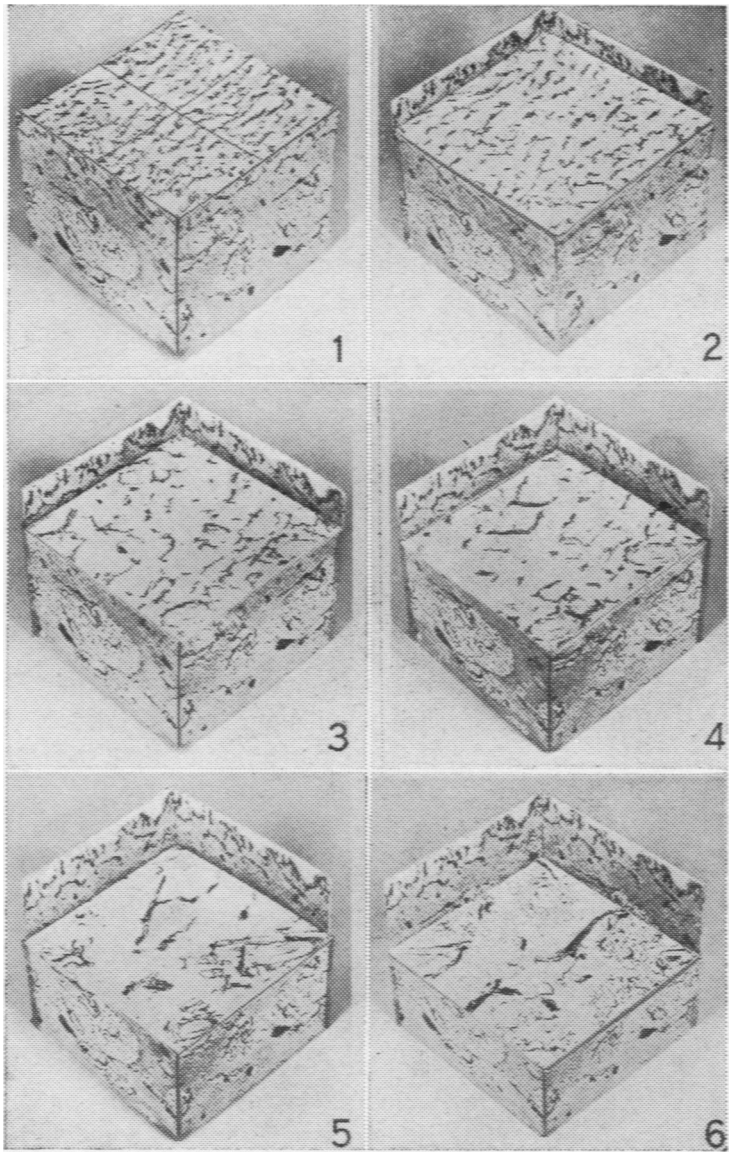
It was observed in ordinary histological preparations that the appearance of the capillaries in the dermal papillae of the body skin of the pig is similar to that in corresponding regions of man. In recognition of the fact that it is difficult or impossible to get an accurate impression of so complicated a structure as a capillary network by two-dimensional visualization, a modification of the Pickworth technic[4] was employed in order that the dermal blood vessels could be studied in three dimensions.

Maximum cutaneous hyperemia of an area of skin was induced by exposing it for 20 minutes to water at 50°C. After such an exposure the erythrocytes were so densely packed in the distended capillaries that there was practically no loss of blood when the skin was incised. Skin and subcutaneous tissue treated in this way was excised to a depth of 8 mm., fixed in 10 per cent formalin, cut in thick sections, and treated with benzidine.

The benzidine imparted a dark blue color to the contents of the engorged vessels. After skin treated in this manner was cleared, a three-dimensional study of its blood vessels could be made with a binocular microscope.

The appearance of the dermal vessels of porcine skin at various levels below the surface is shown in Text-Figure 2. To prepare this illustration a block of benzidine-treated skin was cut serially and parallel to the surface in sections measuring 50 μ in thickness. Another block of the same skin was cut serially and at right angles to the surface. Photographs were made of both series and the prints were mounted in such a manner as to orient the horizontal sections in relation to the depth below the surface that each represented.

In approaching the surface of the body, blood vessels follow an oblique course through the hypodermis and, after reaching the lower



Text-Figure 2. Series of composite photomicrographs showing vascularization of a block of hyperemic porcine skin which measured 2 by 2 by 2 mm. A series of thick (50 μ) benzidine-treated horizontal and vertical sections were mounted in such a way as to show the distribution of veins, arteries, and capillaries at various levels beneath the surface. No. 1 shows the capillary plexus lying in the most superficial (50 μ) portion of the dermis. No 6 shows the vessels in the most superficial layer of the adipose tissue of the hypodermis.

layer of the dermis, branch horizontally to form multiple inter-venal and inter-arterial anastomoses. From these horizontal plexuses there originate a series of broad vascular loops that penetrate to the mid-

portion of the dermis. Inter-arterial and inter-venal anastomoses between these loops serve to establish a mid-dermal plexus. From this mid-dermal plexus originate numerous hairpin-shaped capillary loops which extend upward into the dermal papillae. These capillary loops anastomose freely with one another and constitute the most superficial or papillary plexus. The capillary communications between the superficial arterioles and venules occur at different levels. Some follow a course that brings them within a few micra of the basal epithelial cells over the tips of the papillae. Still others follow an almost horizontal course to establish communications between the arterioles and venules of the intermediate plexus. At all levels through the dermis there are numerous vascular communications with the mantle-like meshwork of capillaries that surrounds the hair follicles and dermal glands.

As may be seen in Text-Figure 2, the number, size, distribution, and communications of the dermal blood vessels of the pig are remarkably similar to those described by Spalteholz [5] in human skin. The similarity of blood vessels in human and porcine skin was found to be so great that it was with difficulty that one could be distinguished from the other in Pickworth preparations.

It is not intended to imply that the anatomical resemblance between the vessels of human and porcine skin denotes an equal degree of functional similarity. Certainly, the vascularization of both indicates that ample and similar mechanical facilities exist either for the transfer of body heat to the surface to facilitate its dissipation, or for the conduct of surface heat to the interior to raise the internal temperature of the body.

Sweat Glands and Sweating

Several types of glands are encountered in the dermis of the pig and although one of them bears some resemblance to the sudoriferous glands of human skin, it does not secrete a significant amount of sweat.

The fact that the pig does not sweat was verified by a series of experiments in which the water loss from the skin of living pigs was measured at various environmental temperatures, with and without the administration of pilocarpine (Table I).

It was found that the water loss from the skin of a live pig does not differ significantly from that of one that is dead. In a cool environment the water loss per square cm. per minute is approximately the same in man and pig. At higher environmental temperatures the rate of water loss from human skin is tremendously augmented, whereas the corresponding increase in water loss from the skin of a pig is relatively small and is due to more rapid evaporation of tissue water rather than to sweating.

So far as can be judged by anatomical criteria, the pig should be a suitable experimental subject from which to derive certain types of information regarding the effects of heat on human skin. Its various layers are of comparable thickness and structure. Its blood vessels are similar in size, number, and distribution. As will be shown later, its susceptibility and reactions to control episodes of hyperthermia are remarkably similar to those of man.

TABLE I

Rate of Water Loss from Surface of Human and Porcine Skin *

	Water loss (mg. per sq. cm. per minute) during a period of 10 minutes							
	Temp., 21°C.; humidity, 30 to 40%				Temp., 36°C.; humidity, 30 to 40%			
	No. of tests	Minimum	Maximum	Mean	No. of tests	Minimum	Maximum	Mean
Dead pig (lateral thoracic region)	4	0.016	0.026	0.019	4	0.023	0.031	0.027
Live pig (lateral thoracic region) without pilocarpine	5	0.016	0.028	0.021	6	0.020	0.032	0.028
Live pig (lateral thigh):								
Without pilocarpine					4	0.018	0.026	0.024
†With pilocarpine (1 mg. per kg. of body weight)					4	0.021	0.030	0.027
Live man (forearm):								
Subject # 1 (A.R.) without pilocarpine	1			0.027	1			0.180
Subject # 2 (A.M.) without pilocarpine	2	0.028	0.038	0.033	2	0.280	0.360	0.320

* Amount of water loss was determined by accretion in weight of $Mg(Cl\ O_4)_2$ contained in base of weighing bottle during the time that the neck of the bottle was held in contact with the skin.

† Iodine color test negative.

Since a pig does not sweat, allowance should be made for the inability of porcine skin to lose heat through the vaporization of moisture derived from sweating. The significance of heat loss through vaporization of moisture in respect to cutaneous burning will be discussed in greater detail in study IV of this series.[6]

Thermal Exposures of Porcine Skin

Closely clipped young (8 to 10 kg.) white pigs were used. It was found that the skin of the pig was not uniformly susceptible to thermal injury. That covering the ears, thighs, buttocks, and ventral surface was more, and that of the neck and midportion of the back less vulnerable, than was the skin of the lateral portion of the shoulders, thorax, and abdomen. The largest uniformly reacting area was the lateral body surface beginning anterior to the thighs and extending forward over the shoulders.

TABLE II

Time-Surface Temperature Thresholds for Thermal Injury of Porcine Skin

Temperature in °C.	Time		Number of experiments	Sub-threshold exposures				Threshold and supra-threshold exposures	
				1° reactions				2° and 3° reactions	
				Hyperemia only		Focal epidermal necrosis		Complete epidermal necrosis	
	Minutes	Seconds		Mild	Severe	Scaling	Small ulcers	Red burn	Pale burn
44	420		1					x	
45	150		1	x					
	180		1					x	
46	45		1	x					
	60		1		x				
	90		1					x	
46.5	45		1	x					
	60		1					x	
47	35		1	x					
	45		1					x	
	50		1					x	
	60		1					x	
48	10		3	x					
	12		1		x				
	14		2			x			
	14		1					x	
	15		2					x	
	16		1		x				
	18		1					x	
	20		1					x	
52	2		4					x	
Cont.	3		1					x	
53		20	1	x					
		30	1		x				
		45	2			x			
	1		2					x	
	1	30	3					x	
	2		1					x	
54		15	1	x					
		25	1		x				
		35	1					x	
55		5	1	x					
		10	1	x					
		15	1	x					
		20	1			x			
		25	1					x	
		30	3					x	
56		10	1			x			
		15	1					x	
		20	1					x	

49	3		4	x					
	4		5	x					
	5		2	x					
	6		5		x				
	6		2			x			
	6		2				x		
	7		2		x				
	7		1			x			
	7		1				x		
	8		4			x			
	8		1				x		
	8		2					x	
	9		11					x	
	10		5					x	
50	1		1	x					
	2		1	x					
	4		1			x			
	5		1		x				
	5		3			x			
	5		2				x		
	5		2					x	
	6		2					x	
	6	30	2					x	
51		45	2	x					
	1		2	x					
	1	30	2	x					
	2		1			x			
	3		2		x				
	3		2			x			
	3		2					x	
	4		2					x	
	5		1				x		
	5		1					x	
	10		2					x	
52		30	1	x					
		45	1		x				
	1	30	1					x	
58		5	1	x					
		10	1					x	
60		2	1	x					
		2	1			x			
		3	1			x			
		5	1					x	
		7	1				x		
		7	1					x	
		10	2					x	
	10		1					x	
65		1	1	x					
		2	1					x	
		3	1					x	
	10		1					x	
70		1	2					x	
		2	1					x	
	3		2						x
75		1	1					x	
		5	1						x
80		1	1					x	
		5	1						x
85		1	1					x	
		5	1						x
90		1	1					x	
		5	1						x
95		1	1					x	
		3	1						x
100		1	1					x	
		3	1						x

The results of 179 exposures of pigs' skin with temperature and duration of each are shown in Table II. All animals were first anesthetized by intraperitoneal injection of pentobarbital sodium.

The surface temperatures at which these exposures were made ranged between 44° and 100°C. The duration of exposures varied between 1 second and 7 hours. The majority of the exposed sites were kept under observation until the reaction had subsided or the lesion had healed. In the case of borderline reactions, duplicate exposures were made and the areas excised at the end of 24 or 48 hours for microscopical study. As indicated in Table II, a wide variety of reactions was observed. These ranged in severity from evanescent erythema to deep necrosis.

It was found that all exposures fell into one of two groups according to whether they had caused full-thickness destruction of the epidermis over the entire target area. Those that failed to cause complete trans-epidermal necrosis were designated as sub-threshold. Those that resulted in complete trans-epidermal necrosis were designated as threshold or supra-threshold depending on whether they were just sufficient or more than sufficient to destroy the epidermis.

Reactions to exposures that were of insufficient intensity or duration to cause complete destruction of the epidermis were designated as first degree. In the mildest of these, the total response to the episode of hyperthermia was evanescent dilatation of superficial cutaneous blood vessels. In others, the hyperemia was more intense and prolonged. In still others, the occurrence after a few days of excessive exfoliation or focal ulceration indicated that some of the exposed epidermis had sustained irreversible injury.

Cutaneous reactions indicative of full-thickness destruction of epidermis over the entire target area were designated as second or third degree according to the depth to which irreversible injury was estimated to have occurred. If the clinical course or microscopic appearance of a lesion indicated that trans-epidermal necrosis had occurred without a significant amount of irreversible damage to the dermis, the reaction was designated as second degree. The more any given exposure exceeded in either duration or intensity the threshold at which the epidermis was destroyed, the greater the depth to which the dermis was affected. Reactions indicating that a significant degree of irreversible injury to the dermis had occurred were designated as third degree. In all second and in many third degree reactions the burned skin was visibly hyperemic for many days. In some third degree reactions the surface of the burn became immediately ischemic and re-

mained so until the pale and necrotic layer of superficial tissue was detached.

In the beginning there was some difficulty in the establishment of clinical criteria by which to predict the ultimate severity of certain injuries. Although there was no difficulty in recognizing almost immediately the difference between a reaction of which the total effect was a mild and transient erythema and one that consisted of deep coagulation necrosis, it was not always possible during the first few days to recognize by clinical observations whether a given lesion represented a severe first degree reaction with incomplete or focal epidermal destruction or a relatively mild second degree reaction.

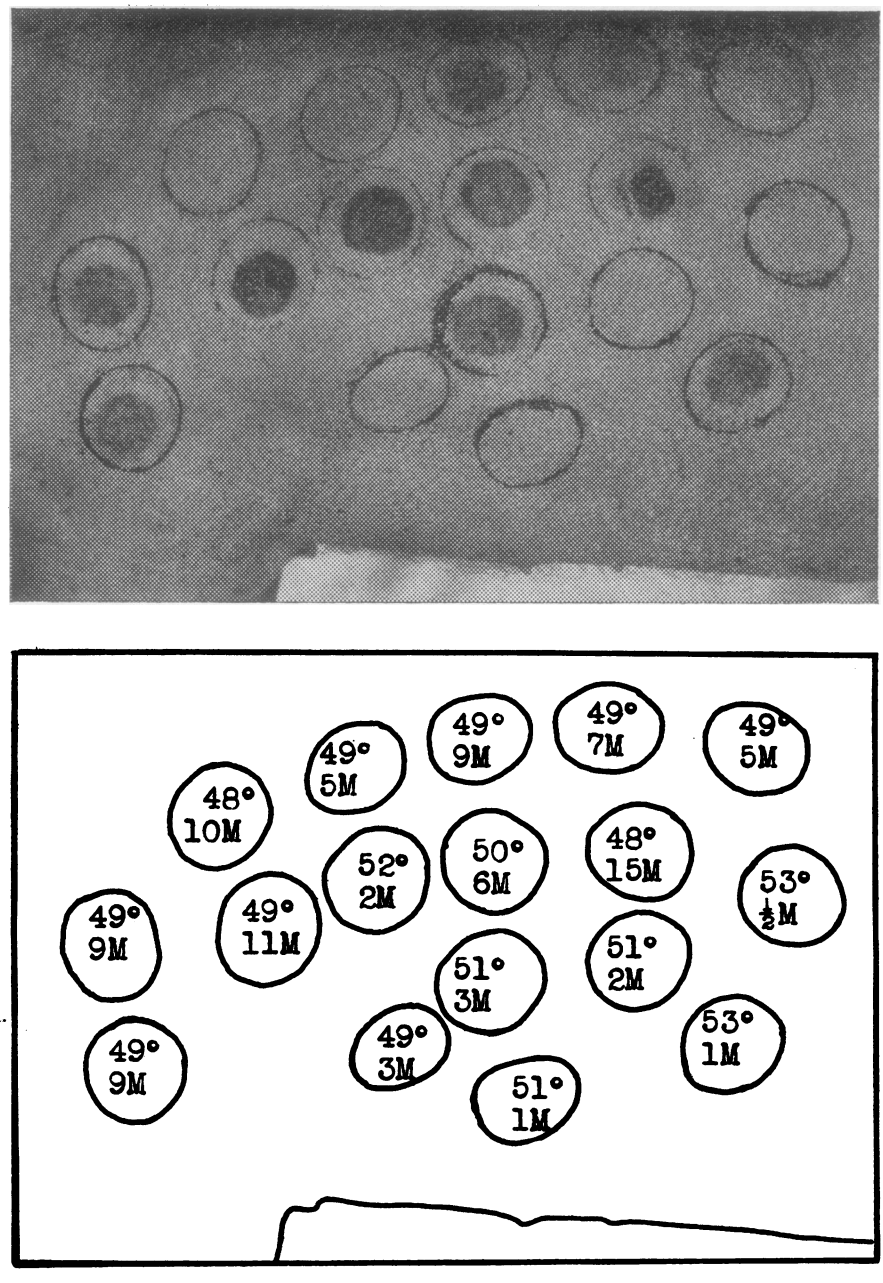
Apart from the microscopic appearance, the most reliable criteria by which to recognize trans-epidermal necrosis were (a) the ease with which dead but still intact epidermis could be displaced by friction on the second and third days after exposure, and (b) the development of complete encrustation of such a lesion within a week.

The macroscopic appearance of different degrees of cutaneous reaction to hyperthermia may be seen in the photographs of the right and left sides of pig 924 in Text-Figure 3, made when the lesions on the right side were 24 hours old and those on the left were 7 days old. It is apparent from these photographs that the duration of exposure at any given temperature was remarkably critical in relation to the kind of reaction evoked. It is equally apparent that the time required to produce a given degree of reaction varied inversely with the temperature.

Experiments on Human Subjects

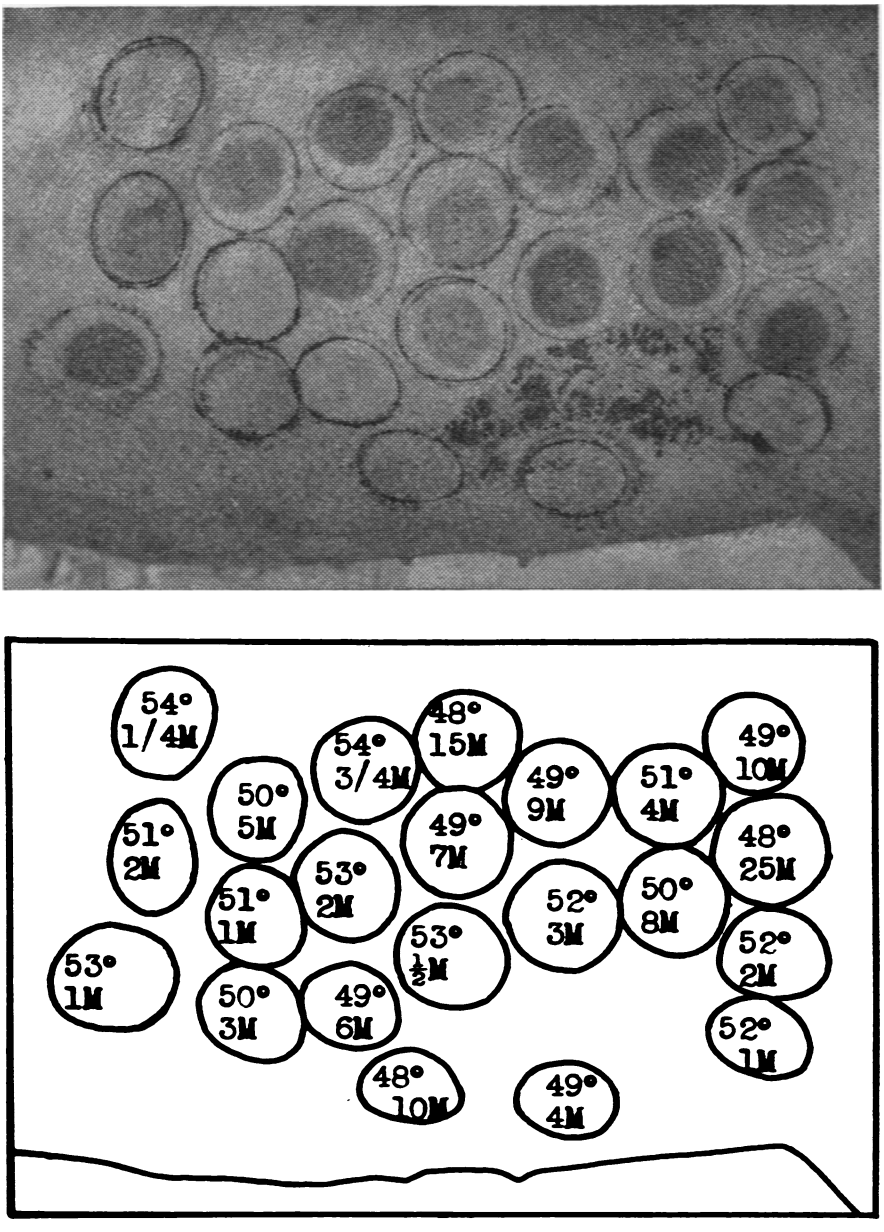
In order to determine the extent to which the results of experiments on pigs were applicable to man, a series of 33 exposures were made on human volunteers (Table III). In some the heat was applied to the skin of the anterior thoracic region and in others to the ventral aspect of the forearm. The exposures were made with the apparatus shown in Text-Figure 1.

As in the pig, the reactions of human skin to hyperthermia were designated as first, second, or third degree. Reactions characterized as first degree were those in which part or all of the epidermis escaped irreversible damage. At one extreme a first degree reaction consisted of nothing more than transient hyperemia. At the other, the erythema was more severe and prolonged and was followed by the formation of miliary vesicles which did not coalesce. Lesions in which there was complete necrosis of the epidermis over the entire target area were designated as second or third degree reactions, depending on the depth



Text-Figure 3-a. Photograph and diagram of burns on the left side of a pig, with the temperature and duration of exposure indicated. Lesions are 7 days old.

to which the dermis appeared to have been destroyed. As in the experiments on pigs, a threshold exposure represented the shortest time at any given temperature that caused complete destruction of the epidermis.



Text-Figure 3-b. Photograph and diagram of burns on the right side of a pig, with the temperature and duration of exposure indicated. Lesions are 24 hours old.

That a given exposure of human skin had resulted in trans-epidermal necrosis was usually, but not always, recognized by early and complete vesication of the target area. Although vesication indicated that the epidermis had been destroyed, absence of vesication did not always indicate epidermal survival. In several instances trans-epidermal necrosis occurred without vesication after supra-threshold exposures.

The explanation of this phenomenon will be discussed subsequently in relation to the pathogenesis of burns.

Discomfort in the form of a stinging sensation occurred between 47.5° and 48.5°C. and was felt more intensely by some subjects than

TABLE III

Time-Surface Temperature Thresholds for Thermal Injury of Human Skin

No.	Temp. at surface in °C.	Duration of exposure			Sub-threshold exposures	Threshold and supra-threshold exposures	Subject	Date
					1° reactions	2° and 3° reactions		
		Hours	Minutes	Seconds	Hyperemia without loss of epidermis	Complete epidermal necrosis		
1	44	5			x		BF	2/6
2*		5			x		BF	2/23
3		6				x	BF	2/6
4*		6				x	BF	2/23
5*	45	2			x		KL	2/16
6*		3				x	KL	2/3
7		3				x	HA	2/4
8*	47		18			x	RK†	2/13
9*			20		x		KL	2/25
10*			20		x		AM	2/26
11*			20		x		PG	2/26
12			25			x	RK†	1/8
13*			40			x	AM	2/26
14			40			x	PG	2/26
15			45			x	RK†	1/8
16	48		15		x		PG	7/19
17			15			x	AR	7/19
18			18			x	AM	6/26
19*	49		8		x		AM	2/16
20			8		x		AM	6/26
21			9	30		x	AM	6/26
22*			10			x	AM	6/26
23			11			x	AM	6/26
24			15			x	AM	6/26
25	51		2		x		AM	6/26
26			4			x	AM	6/26
27			6			x	AM	6/26
28	53			30	x		AM	6/26
29			1	30		x	AM	6/26
30	55			20	x		PG	7/19
31				30		x	AR	7/19
32*	60			3	x		FH	2/1
33*				5		x	FH	2/1

* Oil used instead of water as source of heat.

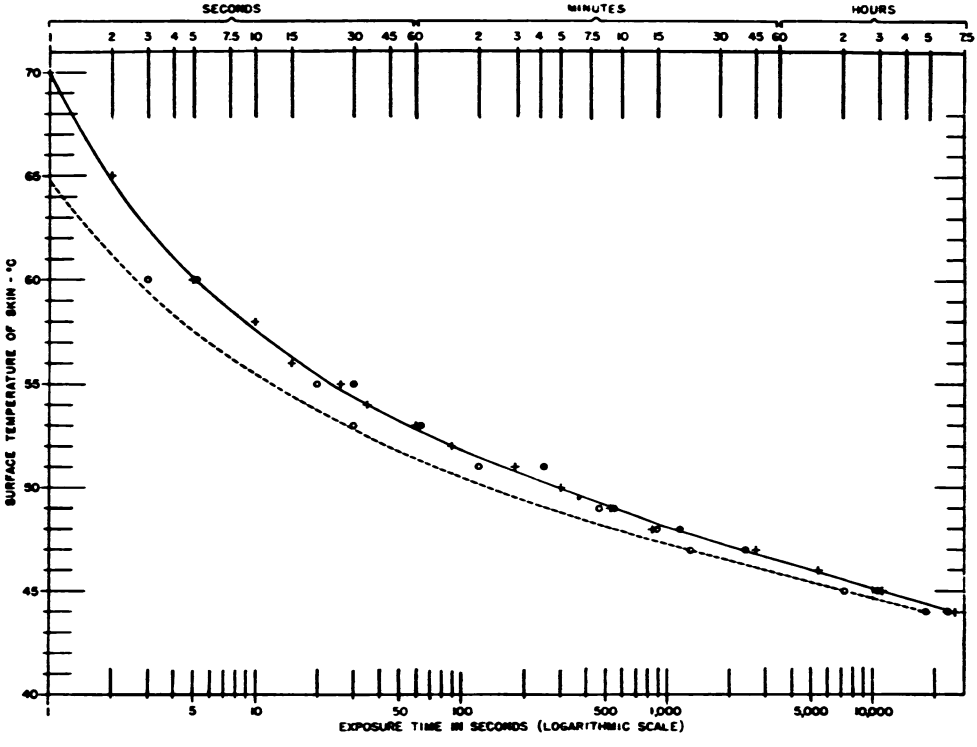
† Subject RK was atypical in that his threshold for thermal injury was significantly lower than that of other experimental subjects.

by others. Severe burns were sustained without discomfort at 47°C. and intense discomfort was sometimes complained of before any irreversible injury had been sustained at temperatures in excess of 48°C.

The results of the human experiments have been summarized in Table III.

Relative Vulnerability of Porcine and Human Skin to Thermal Injury

To facilitate comparison of the data included in Tables II and III, certain of the more critical observations in both have been combined graphically in Text-Figure 4. The solid line was established by points representing the time and temperature of exposures that caused minimal second degree reactions of porcine skin. The points by which this



Text-Figure 4. Time-surface temperature thresholds at which cutaneous burning occurs. The broken line indicates the threshold at which irreversible epidermal injury of porcine skin is first sustained. The solid line indicates the threshold at which epidermal necrosis of porcine skin occurs. Critical exposures of porcine skin are represented by crosses. Each cross denotes the shortest exposure time at the temperature indicated which resulted in trans-epidermal necrosis. The results of critical experimental exposures of human skin are indicated by circles. The open circles represent the longest exposure at the temperature indicated that failed to destroy the epidermis, and the solid circles represent the shortest exposure at the temperature indicated that resulted in trans-epidermal necrosis.

line was established are represented by crosses. Each cross represents the shortest time at the temperature indicated that resulted in trans-epidermal necrosis of the entire target area afer exposure of pig's skin. The more that the time of any given exposure placed it to the right, or that the temperature placed it above the solid line, the greater the

depth to which the skin was destroyed. All exposures that were situated a significant distance above and to the right of the solid line were supra-threshold and all those situated a significant distance below and to the left of the solid line were sub-threshold.

The extent to which the reactions of human exposure corresponded to those observed in the more comprehensive animal experiments is indicated by the open and solid circles in Text-Figure 4. The open circles represent the maximum exposures that failed to destroy human epidermis and the closed circles represent the minimum time at the temperature indicated that resulted in complete destruction of human epidermis.

The broken line in Text-Figure 4 represents the approximate threshold at which the first morphological evidence of thermal damage to porcine epidermis was recognized. Exposures situated below the broken line caused no appreciable injury. Exposures lying between the broken and solid lines resulted in varying degrees of epidermal damage short of trans-epidermal necrosis. Since the reaction of human skin to controlled episodes of hyperthermia was not examined microscopically, no inferences can be drawn as to the precise time at any given temperature at which microscopic evidence of injury to human epidermis was first recognizable.

The results of the two sets of experiments (Tables II and III) indicate that at similar surface temperatures there is little or no quantitative difference in the susceptibility of human and porcine epidermis to thermal injury. The time-surface temperature threshold for the occurrence of trans-epidermal necrosis in man appears to be similar to that for the pig. It may be inferred that the optimal thermal milieu of the epidermal cells of both man and pig lies within a few degrees of the temperature that is normal for their internal tissues and that any rise in epidermal temperature above that level may be injurious if sufficiently prolonged.

The lowest surface temperature that was responsible for cutaneous burning in these experiments was 44°C. and the time required to cause irreversible damage to epidermal cells at this temperature was approximately 6 hours. It could be inferred from the contour of the curve (Text-Fig. 4) which represents the injury-producing threshold that burning would probably have occurred at even lower temperatures if the experiments had been sufficiently prolonged. The rate at which irreversible cellular injury was sustained increased rapidly as the surface temperature was raised, and for each degree rise in surface temperature, between 44° and 51°C., the time required to produce such injury was reduced by approximately one-half.

Above 51°C. the rate of injury began to fall off and the time-temperature curve depicting the threshold at which trans-epidermal necrosis occurred tends to become asymptotic in relation to the temperature axis. Below 44°C. there was a rapid decrease in the rate at which burning occurred and the time-temperature curve depicting the threshold for burning becomes asymptotic in relation to the time axis.

Through reference to Text-Figures 1 and 2 in Study III,[3] it will be apparent that the change in trans-epidermal temperature caused by exposing the surface of the skin to excessive heat is comprised of two phases. The first represents the time required to satisfy the thermal capacity of the epidermis or the transfer of a sufficient amount of heat energy to establish a stabilized trans-epidermal gradient. Thirty seconds was ordinarily sufficient for the attainment of a steady state of heat transfer in which the temperature at the basal cell level was only slightly lower than that at the surface. The second phase represents that part of the hyperthermic episode in which the trans-epidermal temperature gradient was stabilized.

Thus, in the case of surface temperatures under 51°C. the time required to cause irreversible injury of the epidermis was so long in relation to the amount of time required to bring the temperature of the basal cell level to a steady state that the latter was negligible. The total exposure time required to destroy the epidermis at such surface temperatures was essentially identical to the total duration of the steady thermal state within the epidermis, and under these circumstances there was a linear relationship between time and surface temperature in the production of burns between 44° and 51°C.

The reason that this linear relationship did not prevail below 44°C. probably was due to the increased effectiveness of the cellular reparative processes as the hyperthermic level approached the temperature range that was normal for the tissue.

As surface temperature rose above 51°C. and the total periods of exposure were shortened, the 30 seconds required to stabilize the epidermal temperature came to represent a progressively larger proportion of the entire hyperthermic episode. There was no longer the same kind of relationship between the surface temperature and that at the basal cell level as existed with the longer exposures and there was a progressive deviation from the linear relationship of surface temperature and time that characterized the injury curve between 44° and 51°C.

It should be borne in mind that these data refer to surface rather than to environmental temperature and it is not intended to imply that identical circumambient temperatures necessarily result in identical

surface temperatures of human and porcine skin. The only inference that is justified is that at any given surface temperature the time required to destroy porcine epidermis is approximately the same as that required to destroy human epidermis.

A mathematical analysis of these and other data and a consideration of their significance in relation to the rate processes of other physicochemical phenomena are included in Study V of this series.[7]

Vulnerability of Ischemic Skin to Thermal Injury

One of the reasons that exposure of the skin to a running stream of hot water was the method of choice in these experiments was the belief that by this technic there would be no mechanical interference with the circulation of blood through the dermal capillaries. All of the foregoing exposures were made at atmospheric pressure. It was believed that circulation of relatively cool blood through the dermal capillaries probably would tend to protect the skin against burning and that to be applicable to field conditions data on the tolerance of skin to hyperthermia should be derived from the reactions of physiologically normal tissue.

In order to determine the extent to which local impairment in blood flow may increase the vulnerability of the epidermis to thermal injury, the following experiments were undertaken.

A control series of burns was made on each of 3 pigs by exposing various skin sites to running water at atmospheric pressure. The predetermined time and temperature of each exposure was such that severe first degree or mild second degree reactions could be anticipated (Table IV).

It was found that all 7 minute exposures at 49°C. and all 2 minute exposures at 51°C. made at atmospheric pressure were sub-threshold in the sense that they failed to cause complete trans-epidermal necrosis. That they were close to threshold was indicated by the fact that all 9 minute exposures at 49°C. and all 4 minute exposures at 51°C. did cause trans-epidermal necrosis.

Having established the position of the threshold for trans-epidermal necrosis in these animals to be between 7 and 9 minutes at 49°C. and between 2 and 4 minutes at 51°C. for exposures made at atmospheric pressure, a second series of exposures was now made in which the water pressure was increased by an amount corresponding to 80 mm. of mercury. With this pressure on the surface of the skin during the time that it was exposed to heat, there was no instance in which the reaction to a 7 minute exposure at 49°C. or to a 2 minute exposure at 51° C. was increased in severity.

It is apparent from the data summarized in Table IV that the application of pressure sufficient to collapse superficial dermal capillaries during a period of exposure does not cause appreciable augmentation in the vulnerability of epidermis to thermal injury.

In view of the extreme thinness of the epidermis, these results were to be expected. For reasons discussed in Study I of this series,[8] the temperature of the basal cell layer of the epidermis is determined primarily by the temperature of the surface. Thus, the dermal tem-

TABLE IV

Effect of Thermal Exposures with and without Pressure Ischemia

Animal no.	Temperature	Duration of exposure	Excess pressure on skin	No. of exposures made	Number of lesions	
					Without trans-epidermal necrosis	With trans-epidermal necrosis
	(°C.)	(*minutes*)	(*mm. Hg*)			
887	49	7	0	5	5	0
	49	9	0	5	0	5
	49	7	80	5	5	0
899	49	7	0	4	4	0
	49	8	0	4	2	2
	49	9	0	4	0	4
	49	7	80	4	4	0
	49	8	80	4	3	1
901	51	2	0	3	3	0
	51	3	0	3	2	1
	51	4	0	3	0	3
	51	2	80	3	3	0
	51	3	80	3	1	2

perature gradients, which may be appreciably altered in ischemic as compared to normal skin during thermal exposure, would have little effect on the time-temperature relationship that exists at the epidermal-dermal interface.

LATENT THERMAL INJURY AND THE CUMULATIVE EFFECTS OF REPEATED SUB-THRESHOLD EXPOSURES

When the data summarized graphically in Text-Figure 4 are recalled, it is apparent that morphologic cellular alterations occurred only during the terminal phase of sub-threshold exposures. Not until the duration of any given episode of hyperthermia was such as to bring it to the level indicated by the interrupted line in Text-Figure 4 was there recognizable evidence of epidermal injury. This phenomenon is even more readily apparent in the photographs shown in Text-Figure 3. In these it may be seen that the 7 minute exposure at 49°C. on the left side of the animal shows only a trace of residual erythema whereas

TABLE V

The Cumulative Effects of Repeated Sub-Threshold Thermal Exposures on the Skin of the Pig*

Duration of each exposure	No. of exposures at same site	Interval between exposures	Effect of exposure on skin				Reference no.
			No evidence of epidermal injury		Epidermal necrosis		
			Mild vascular reaction	Severe vascular reaction	Focal	Complete and irreversible	
(minutes)							
3	1		x				1
3	1		x				2
3	1		x				3
4	1		x				4
5	1		x				5
6	1			x			6
6	1			x			7
6	1			x			8
7	1			x			9
7	1				x		10
8	1				x		11
8	1				x		12
8	1					x	13
9	1					x	14
9	1					x	15
9	1					x	16
9	1					x	17
9	1					x	18
3	3	3 min.				x	19
3	3	3 min.				x	20
3	3	3 min.				x	21
3	3	6 min.				x	22
3	3	12 min.				x	23
3	3	24 min.				x	24
3	3	48 min.				x	25
3	3	48 min.			x		26
3	3	72 min.			x		27
3	3	72 min.			x		28
3	3	96 min.			x		29
3	3	120 min.		x			30
3	3	240 min.	x				31
3	3	24 hrs.	x				32
3	3	48 hrs.	x				33
2	5	2 min.				x	34
2	5	30 min.	x				35
2	5	60 min.	x				36
3	2	12 min.		x			37
5	2	60 min.				x	38
5	2	240 min.			x		39

* All exposures were made to water at 49°C.

both of the sites of 9 minute exposures at that temperature show trans-epidermal necrosis. Does this indicate that no epidermal injury had been sustained during the first 7 minutes, or does it mean that injury was present but unrecognizable?

In order to gain more information concerning this point, the experiments summarized in Table V were undertaken. Thermal expo-

sures were made with a running stream of hot water at 49°C. and at atmospheric pressure. Three young pigs were used.

The first series of exposures (reference nos. 1 to 18) were for control purposes and served to establish the reproducibility of reactions to single exposures at this temperature. It may be seen that there was not a single instance in which an exposure for less than 7 minutes caused recognizable necrosis of the epidermis, and that in every instance in which exposures as long as 9 minutes were given there was complete necrosis of the epidermis. Skin sites receiving 7 minute exposures recovered with incomplete or no damage to the epidermis, whereas skin sites receiving 9 minute exposures underwent complete ulceration.

The control exposures were followed by a series (nos. 19 to 39) in which repeated exposures, individually incapable of causing recognizable epidermal injury, were applied to the same area. It was found, for instance, that although a single 3 minute exposure at 49°C. caused no recognizable change in the epithelial cells, three such exposures separated by recovery periods as long as 24 minutes had the same total destructive capacity as a single continuous 9 minute exposure.

It was clear that a certain amount of epidermal injury was sustained during the first 3 minutes and that at least 24 minutes were required before there was an appreciable recovery from this injury. That complete recovery occurred after a period of 2 to 4 hours was indicated by experiments 30 and 31.

Experiments 34 to 39 showed what might have been expected; namely, that recovery from the latent injury of a 2 minute exposure was more rapid and that from a 5 minute exposure less rapid than was the case after a 3 minute exposure.

Further discussion of the implications of these experimental results will be found in Study V of this series.[7]

Summary

The reciprocal relationships of surface temperature and duration of hyperthermia in the production of cutaneous injury have been investigated for pig and man. The data were derived from experiments in which the surface of the skin was brought immediately to, and maintained at, a constant hyperthermic level in such a manner that there was no external mechanical interference with the flow of blood through the skin.

Although there were certain qualitative differences in the reactions of human and porcine skin to excessive heat, there were no significant quantitative differences in their susceptibility to thermal injury in these circumstances.

Time and Temperature in Relation to the Occurrence of Cutaneous Burning

In order to characterize any episode of hyperthermia as critical in respect to its capacity to destroy the epidermis, it is necessary to know both the intensity and the duration of the exposure. When the temperature of the skin is maintained at 44°C., the rate of injurious change exceeds that of recovery by so narrow a margin that an exposure of approximately 6 hours is required before irreversible damage is sustained at the basal cell level. At surface temperatures of 70°C. and higher, the rate of injury so far exceeds that of recovery that less than 1 second is required to cause trans-epidermal necrosis.

At surface temperatures between 44° and 51°C., the total exposure time required to destroy the epidermis is essentially identical to the total duration of the steady thermal state within the epidermis, and, under these circumstances, the rate at which burning occurs is almost doubled with each degree rise in temperature.

Below 44°C. there is a rapid decrease in the rate at which burning occurs and the time-temperature curve is asymptotic in the direction of the time axis. This is probably due to the increased effectiveness of the cellular reparative processes as the hyperthermic level approaches the temperature range that is normal for the tissue.

At surface temperatures greater than 51°C., the exposure time required to destroy the epidermis is so short that during most or all of it the deeper layers of cells are in the process of being brought to, rather than being maintained at, a state of thermal equilibrium with the surface. Thus, as the surface temperature is raised above 51°C., the rate of injury begins to fall off and a time-temperature curve depicting the threshold at which trans-epidermal necrosis occurs is asymptotic in the direction of the temperature axis.

The minimum time required to destroy the epidermis at surface temperatures above 70°C. was not determined. It was observed, however, with exposures at flame temperatures (over 1000°C.), that the amount of time required to raise the temperature at the epidermal-dermal junction to a cell-killing level is so brief that the interposition of anything capable of impeding heat transfer to the skin may be sufficient to make the difference between burning and absence thereof.

Compressive Hyperthermia

Although pressure may increase the rate of heat transfer to the skin, and thereby the rate of burning, by improving the interface contact between it and a solid hot object, there was no evidence that compressive

occlusion of dermal blood vessels has any effect on the susceptibility of the epidermis to thermal injury. When hot water was applied to the surface of the skin at different pressures, it was observed that compressive ischemia did not alter the rate at which burning occurred. It was concluded that the conduction of heat energy away from the skin surface by way of the blood stream does not afford a significant degree of protection against epidermal injury.

Color of Cutaneous Burns

Compression of the skin during exposure to heat may alter the surface color of the resulting burn without affecting its severity. Within a certain range of surface temperature, the application during the exposure of sufficient pressure to blanch the skin may cause a burn to remain ischemic that would otherwise be hyperemic. In such circumstances, differences in color are not indicative of differences in the depth of the injury.

In burns produced without concomitant compression of the skin, the color of the surface of the burn is determined in part by the rapidity and degree of the initial increase in dermal temperature and in part by the duration of the exposure. The surface color of such burns is not a useful criterion for estimating either the severity of injury or the amount of blood that may be pooled in the underlying tissue. When the temperature of the dermis is raised slowly, the superficial vessels become engorged and retain their blood even though the tissue is subsequently coagulated by progressive increase in the intensity of the hyperthermia. When the initial rise in dermal temperature is rapid and high, the superficial vessels contract so quickly that there is no opportunity for them to become hyperemic. Although such burns are superficially ischemic, there is intense hyperemia of the more deeply situated vessels.

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