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The Effect of Local Heat Application on the Human Skin

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THE EFFECT OF LOCAL HEAT APPLICATION ON THE HUMAN SKIN

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A. Introduction

If heat is applied to small skin areas a great variety of reactions may result. For the purpose of experimental study these can be grouped as follows:

1. Sensations, such as heat and pain.
2. Injury reactions, such as skin flare, macules, papules and blisters.
3. The local sweating response.

Studying each group and each phenomenon separately it is hoped "to find the mechanism of each single reaction and the meaning, the part played by the reaction in the delicate regulation by which the organism and the organs are adapted to the ever changing environmental conditions." (August Krogh 82)

The need of such an investigation in the field of injury and particularly the heat reaction was underlined recently by the finding (13) that the pattern of injury reactions to heat is changed in patients with malignant neoplastic disease; however these observations were a chance finding. The first step of a scientific approach is the determination of the normal reaction pattern and the illumination of the physiological mechanism of the various reactions. "Science is built with facts as a house is with stones; but a collection of facts is no more a science than a heap of stones is a house." (Poincaré 109) The attempt to obtain a new and better understanding of the physiological nature of these reactions rather than the mechanical collection of data largely determined the scope of this study. For instance skin flare is of great physiological interest, because it involves a vascular reaction and a nervous reflex. Therefore skin flare was studied with considerable detail. The

formation of a blister comes more in the field of pathology than physiology, and so this was treated briefly. Excluded from detailed description were experiments which did not produce conclusive or new information.

Heat as a means of injury production has the advantage over other injurious agents in that it can be easily controlled and measured. In these experiments most of the experiments are done at threshold levels, i.e. the lowest level of stimulation where a definite reaction can be obtained. The great sensitivity of these determinations make it necessary to use equipment which could be controlled accurately.

In addition to the control of the stimulation it is necessary to control and determine the influence of other factors on the injury reaction. These fall naturally into two groups:

1. Changes of the external environment, such as environmental temperature and relative humidity.
2. Changes of the internal environment, such as blood flow and nervous factors.

The experiments are limited to human subjects. This was done to obtain comparative data for various subjective and objective phenomena, as pain and injury; and also to avoid erroneous conclusions by application of results obtained in animal experiments to human physiology.

B, Review of Literature

Although few correlative studies have been made, in the areas discussed here, and although no review has been published encompassing this field, there is a considerable number of publications dealing with some of the particular reactions. This makes it necessary to treat each subject separately, even though this will involve a certain amount of repetition.

a) The physical and biophysical basis of heat absorption,
heat transmission and heat distribution.

The physical aspects of heat and its effects are well covered by McAdams' book on heat transmission (97). The American Institute of Physics in 1941 published a book on "Temperature and Its Measurement" (1) which combines the physical as well as the biophysical aspect. Glasser's "Medical Physics" (51) and Newburgh's book on "The Physiology of Heat Regulation and the Science of Clothing" (103) give detailed discussions of the various biophysical factors involved in the absorption and transmission of heat in the skin.

The normal skin temperature in various regions of the human body was measured by Benedict (12) in 1925. His findings were confirmed and amplified by Cobet (28), Foged (43), Mendelsohn (99) and Sheard (124). The temperature gradient across the skin was determined by Bazett and McGlone (7) by means of loop thermocouples placed at various skin depths. With the same methods these two investigators determined the changes of skin temperature necessary to produce the sensations of heat and cold (5,8). They found that an increased blood flow to the skin increases the thermal capacity and the thermal conductivity of the tissues. The increase of heat capacity decreases the amount of heat energy input required to obtain and maintain any given temperature. The increased heat conductivity increases the requirement of heat energy input. These two factors then affect heat energy in opposite directions and according to the authors balance each other.

Danforth (32) in 1930 using radiant heat of various wave lengths determined its penetration through the tissues of the cheek. Fourteen to twenty-one per cent of the total heat energy penetrated the 5 mm thickness of living tissue for the wave lengths of 0.6 - 1.4 μ , respectively. The

classical work on the effect of radiation on the tissues comes from Bachem and Reed (3) who carefully determined the amount of absorption transmission in each skin layer for each range of the total radiation spectrum. Hardy and Muschenheim (59) in 1936 while working on radiation from the human body, determined the absorption characteristics of the skin and came to conclusions which essentially confirmed the previous work. Henriques and Moritz (65) and Buettner (19) discuss in detail the physical basis of heat absorption and heat transmission in an attempt to explain the cause and the nature of thermal injury. Hensel (68) recently performed some excellent work on the transfer of contact heat. Using subcutaneous thermocouples whose depth in the skin was controlled by micrometer measurements, he found a normal heat gradient across the skin of $0.2 - 0.5^{\circ} \text{C}$ per mm up to a depth of 1.5 mm. By suddenly raising or lowering the surface temperature of the skin he determined the heat conduction ratio for the various layers.

Advantages and disadvantages of the use of thermocouples in the determination of epidermal and subcutaneous temperatures were studied by Stoll and Hardy (131) and by Whyte and Reader (143). Lately Osserman and Minard (104) designed a method of studying heat flow into the skin and within the skin. A small ring is sealed to the skin through which a steady stream of water is passed, the water being in direct contact with the skin. By measuring the rate of flow of the water and the temperature before and after contact with the skin, the actual heat loss to the skin per unit of time is determined. The movement of heat within the skin was determined with an intradermal flow meter. This method indicates the blood flow in the skin and it is so sensitive that it is possible to register the intradermal pulse. No physiological results have been published as yet.

b) The sensations of heat and heat pain.

The problem of what causes and what constitutes a sensation is one of the oldest and one of the most discussed in the physiological literature. The names of Weber, Fechner, Hering, Ebbecke, and Head and Holmes are among the prominent scientists who have worked in this field. As the general background is amply discussed in physiological textbooks it is not necessary to amplify on this aspect of the problem at this time. The specific applications of these theories to our problem are given by Lewis (95) in his book on "Pain", in the report of the Association on Nervous and Mental Diseases (111), in Wolff's review of pain (151), and in Ogilvie's book on "Pain and Its Problems" (103).

The first research worker who left the field of theoretical discussion and began practical experiments on heat sensation and heat pain was Sir Thomas Lewis (88). Using a heated copper bar, which had a contact area with the skin of $4/5$ square inches, he found that the epidermal pain threshold was 43° C with a subcutaneous temperature (1 mm depth) of 38° C. The point of intolerable pain was 48.7° C for epidermal, and 42.5° C for subcutaneous temperature. Bazett and McGlone (5,8,9) found by means of subcutaneous needle thermocouples that the depth of temperature receptors for warmth was 0.6 mm and that the cold receptors were at a depth of 0.15 mm. In 1926 Schriever (122) made some observations which have neither been confirmed nor contradicted. Using a heated platinum wire loop he determined pain sensation by layerwise anaesthetisation of the skin and observed that pain could be elicited from all skin layers.

Outstanding work on pain during the last twenty years has been done at Cornell University by J. D. Hardy, H. G. Wolff and their coworkers, S. Wolff, H. Goodell, C. Muschenheim, G. A. Schumacher, T. O. Oppal and C. Torda (33,59,60,61,62,63,131,151,152). Their concept is that the

energy output of the stimulating instrument determines the nature and the intensity of the ensuing sensation. This idea has penetrated into most physiological textbooks. They used a small radiation source and demonstrated that heat and heat pain do not show spatial summation unless the area of exposure is smaller than 0.3×0.3 cm. They concluded from their data that the gradient across the skin is proportional to the radiation intensity and therefore feel justified in neglecting it. They define the sensation of warmth in terms of heat intensity with a threshold of 0.00015 Gm. cal. per cm^2 per 3 seconds. The pain threshold is 0.218 Gm. cal. per cm^2 per 3 seconds, or 1900 times that for heat sensation. This concept was accepted by many investigators, but recently some contradictory evidence has appeared in the literature (vide infra). Without officially revoking the older theory, Hardy, in a recent article (63), accepted the idea that a definite skin temperature is critical for pain sensation.

Woollard and coworkers (153) studied the neurohistological basis of cutaneous pain and found that pain can be aroused from the deeper layers of the epidermis and from the superficial layers of the dermis. Wedell (141) and Bishop (15,16) approached the subject from the anatomical point of view and came to similar conclusions. Buettner (19) is one of those who maintain that there is an absolute temperature threshold for pain, which he puts at 44.8° C and at a depth of 0.1 mm. Gregg (54) accepts Wolff and Hardy's concept. He finds spatial summation for heat sensation to exist but not for pain. Whyte in 1951 (144) uses radiation heat to determine the pain threshold and concludes that there is an absolute skin temperature threshold for pain sensation. He found the threshold for pricking pain to be 46.58° C and that for intolerable pain, 48.28° C. Recently Wertheimer and Ward (142) also found that pain is a function of an absolute skin temperature; and Cook (29) using microwaves and infra-red-radiation arrived at the same conclusion.

There is no doubt, now, that temperature sensation is physiologically separate from pain sensation. Repeatedly it has been demonstrated that one can be lost while the other is unaffected. Although separate, the two have many similarities.

Hahn (57,58) in 1927 stated that the degree of temperature change and the speed of change do not affect the intensity of the temperature sensation, only the absolute temperature determining the character of the ensuing sensation. Subsequently for many years the views of Wolff and his group dominated (60,63,131). They thought that the sensations of warmth and pain were a function of the heat energy and could be expressed in the same units, the only difference between the two sensations being one of degree. O'Connor (102) studied the origin of the sensations of heat and cold and found that the intensity of sensation depended on the degree of change per unit of time. Recently Hensel (67,68,69,70) in a series of carefully planned experiments reexamined Wolff and Hardy's theory of temperature sensation. If heat is applied to the skin surface this decreases the natural skin temperature gradient and cooling increases it. Hensel altered the skin gradient by the use of intravenous injections of hot and cold solutions and he obtained heat sensation with the injection of hot solution and cold sensation with the injection of cold solutions. On cats and frogs he determined nerve action potentials under constant heat stimulation and found that these persisted with the same intensity, even when the heat distribution had reached a fully balanced state. Analysing the results of these and other experiments he came to a three-dimensional concept of temperature sensation with three independent parameters: 1. Absolute temperature. 2. The differential quotient of change of temperature with time. 3. The area of stimulation.

c) The skin flare reaction .

According to Lewis (91) an injury should show all components of the triple response, i.e. increased temperature, edema and skin flare. At threshold level it is difficult to demonstrate the first two components, while the skin flare is simply defined and easily determined. Therefore, for the purpose of this discussion, skin flare is to be considered as the criterion of injury.

The phenomenon of skin flare is very interesting from the physiological point of view and it is a much discussed subject. In 1877 Stricker (132) stimulated the posterior roots of a spinal nerve and produced vasodilatation of the innervated area. Goltz in 1896 (52) showed that stimulation of the peripheral end of the cut sciatic nerve can, according to the strength of the stimulus, cause either vasodilation or vasoconstriction. Langley in 1900 (84,85) defined the axon reflex, and Bayliss in 1901 (11) by extirpation of the posterior nerve root and stimulation of the cut sciatic nerve confirmed the previous findings of the axon reflex nature of skin flare. He also coined the expression "antidromic conduction" for the efferent part of this reflex. Bruce in 1910 (18) showed that the inflammatory response is not influenced by denervation unless there is time for nervous degeneration.

Lapinski in 1926 (83) showed that it is possible to produce vasodilatation by stimulation of sympathetic fibres. Krogh three years later (81) explained this as due to decreased physiological tonus of the capillaries instead of active dilatation.

Lewis (88,91,92,94) working on the peripheral mediator of skin flare demonstrated a specific chemical substance which is maintained after

circulatory occlusion and which is independent of the nature of the stimulus. This mediator is thought to be released in the epidermis beneath the horny layer and probably also in deeper parts of the skin and other tissues. Lewis also confirmed the axon reflex nature of the skin flare. But he failed to identify the nerve fibres responsible for this reflex, nor could he determine the vasodilator substance released at the distal end of this reflex. Leriche (87) explains skin flare by the assumption of third order peripheral ganglia, but he could not give any anatomical proof of their existence. Recently Holton and Perry (71) attempted to identify the peripheral effector substance of the antidromic vasodilatation and concluded that it could not be either acetylcholine or histamine. Erci and Uvnaes tried to determine the type of nerve responsible for vasodilation (40,41). They demonstrated that the afferent portion of the chorda tympani of the cat can carry vasodilator impulses. They also claim that skeletal muscle and possibly the heart have a sympathetic vasodilator nerve supply of possibly cholinergic character. Folkow and Gernandt (45,46) showed that there are cholinergic sympathetic fibres in the muscles of the limb which are activated by stimulation of the supraoptic nucleus of the hypothalamus. In these experiments they found a parallelism between action potentials and volume curve. As further support they demonstrated that the dorsal root does not convey centrally induced vasodilator impulses. Another explanation was given by DeLargy, Greenfield and others in 1950 who showed that, in skeletal muscle, epinephrine acts as a vasodilator while nor-epinephrine acts as a vasoconstrictor substance. Therefore, they believe, it is not necessary to assume any cholinergic effects of the sympathetic system. They consider it possible to explain vasodilatation by the relative preponderance of one or the other of the sympathetic mediator substances.

The review of literature quoted above presents many contradictions and it is impossible, from it, to reach definite conclusions. It seems certain that some of the experimental procedures were not adequate to prove a particular physiological mechanism, and it is impossible to decide at present which, if any, are correct. Essentially Lewis' statement (94) still stands: "We do not know quite definitely that vasodilatation is ever provoked naturally through posterior root channels; neither are the fibres that give this response to artificial stimulation positively identified."

d) The reaction to severe injury

The term "severe injury" as used here is only comparative with skin flare. They are not, in the ordinary sense, severe reactions. The reactions considered would no doubt constitute a severe injury if they were produced over a large skin area. With the area of the size injured in our own experiments, and most of those of the other investigators mentioned below, the term severe is purely a relative one.

Observation and study of injury and healing goes back to the Bhagavad Gita of the ancient Hindus and probably even further. But systematical, experimental and scientific studies started only very recently. The outstanding investigator was Sir Thomas Lewis, who some 30 years ago reported a tremendous number of ingeniously contrived experiments. His work and that of his pupils, W. S. Love, R. T. Grant, K. E. Harris and H. H. Marvin, resulted in a large number of publications (88,89,90,91,93,94) including the 1927 book "The Blood Vessels of the Human Skin and Their Responses" (91) and the 1942 book "Pain" (95). Lewis used for his burn experiments a heated copper bar with thermocouples attached, and he

measured subcutaneous temperature with needle thermocouples. His approach is not that of the typical modern investigator who assembles his data; analyses them; and draws conclusions regarding mean values, standards of deviation and significance. Lewis makes a number of single experiments which approach the subject from various aspects. Then he draws his conclusions. It sounds unscientific, and no doubt today scientific journals would not publish this type of investigation. But his work stands very well the test of time. Many carefully planned experiments using complicated methods have only been able to confirm his almost intuitive findings. Lewis considered the threshold for blister formation 51.5°C , with a subcutaneous temperature of 41.8°C .

Hucack and McMaster (73,74,75) in 1932 and 1934 worked on the permeability of the skin vessels in mice, and found that a temperature of 44°C was critical for the production of hyperthermic edema. Barcroft and Edholm (4) determined the influence of immersion in warm water and in cold water for prolonged periods on deep skin temperature and on blood flow. Leach, Peter, Rossiter and Mendelsohn (86,99) worked on experimental burns in pigs and rats utilizing the Thumberg kettle. This is something like a tea kettle and has a contact area with the skin of from 1.5 to 11 mm diameter. It is heated by a steady flow of water and is equipped with a thermometer which records the temperature of the water. Subcutaneous temperature is measured with thermocouples. With three minutes of heat application, 50°C was the critical temperature for an irreversible scab formation, and with one minute, 55°C was the critical temperature. The corresponding subcutaneous temperatures were 41° and 44.8°C , respectively. Henriques and Moritz (65,66) made an extensive study on burn injury in pigs and in human subjects. They originally brought a

flow of hot water into direct contact with the skin. Later they constructed a special heat applicator which consisted of a carefully insulated copper plate which allowed accurate determination of heat loss to the skin. Their observations included a wide range of time and temperature factors. They observed skin flare after five hours at 44° C, and after three seconds at 60° C. Complete epidermal necrosis was obtained after three hours at 44° C, and after five seconds at 60° C. Buettner (19) used radiation heat and thermocouples which were 0.2 and 0.05 mm in diameter and were wound around the arm. Working for the United States Air Force his main interest was in war injuries, their prevention, and the analysis of the physical factors in heat transfer under such conditions, and are not applicable to the problem under discussion.

Local differences of skin reactivity and healing are an accepted clinical fact. However there is no systematic study to support this. The possibility that the skin temperature is a factor in skin reactivity and wound healing was indicated by Ebeling (38), who found experimentally that a rise of 10° C of the skin temperature increased the rate of healing two fold. Fetcher (42) pointed out that the parallelism between skin temperature and blood flow through the skin holds true only in rough outlines. Pollarczek (110) found that ultraviolet light promotes healing in man. Fuke (47) reduced the period of healing by therapeutic thermal radiation.

Various other factors were investigated which do have bearing on the relation of site of injury and wound healing. Arey (2) in his extensive review of wound healing does not mention local differences in the rate of healing. The differential pattern of pain reactivity was determined by Bishop (15), and Strughold (136) who made an analysis of

the density of pain points and the pain-point-pressure over various body regions. Sollman (127), while working on the differential effects of various pharmacological agents, found a difference in local sensitivity in a descending order from back and abdomen to flexor surface of the arm and then to flexor surface of the forearm. Carrell and Hartman (27) gave a scientific basis for the determination of healing by designing a method of accurate measurement of the size of wounds and the decrease of size with time. Du Nouy (34) worked out a complicated formula indicating the affect of area of injury, of the age of the subject, and the individual healing constant on healing time. In addition to the above there is a vast literature on the effect of nutrition on wound healing (especially ascorbic acid), on the effect of metabolism, and on the effect of various hormones (ACTH). As far as the influence of cutaneous site on injury reaction and rate of healing is concerned, there is no systematic study and there is very little factual information which might help in the evaluation and interpretation of such differences.

e) The sweating reaction.

The literature on sweating is quite extensive, much of which is not relevant to the problem of the local heat response. Moreover much of the work is circumstantial with very little direct information on our particular problem.

The peripheral stimulus of sweating was first studied by Langley in 1891. He reported that on sitting in a Turkish bath, generalized sweating started when the mean skin temperature was between 34 - 35° C, which he considers to be 1/2° C above the normal skin temperature. Burn in 1925 (21) was concerned with the innervation of the sweat glands. He found that degeneration of the sympathetic supply did not diminish the

response to pilocarpine in the cat's foot. Degeneration of all nerves produced first increased and later decreased sweating. These changes were correlated to trophic changes of the skin. He showed also that excision of the posterior root ganglion and the adjacent anterior root decreased the sweating response. In 1934 Kuno published what is still the classical book on the physiology of sweating (82). Kuno thinks that the different types of sweat producing stimuli may act on different centres. Psychic stimuli on the cortical centre, thermal stimuli on the subthalamic centres, gustatory stimuli on the bulbar centres, and direct skin stimulation on spinal centres. The existence of these spinal centres he considers as doubtful, and their physiological function as insignificant. But local stimulation by increasing the skin temperature and therewith stimulating the subthalamic centres he considers as important, as generalized sweating can occur with increased cutaneous temperature, even if the body temperature is actually lowered. Experimentally he proved this by exposing subjects to an environmental temperature of 45° C while part of the body was immersed in water of $5 - 10^{\circ}$ C. This caused sweating with lowered body temperature. During the same year Phelps and Vold (108) studied ventilation and found a small positive relationship between environmental humidity and skin temperature, and a more marked positive relationship between air temperature and skin temperature. An increase of 1° C in air temperature caused an increase of 0.27° C in skin temperature, and a corresponding shift of three per cent of total heat loss from radiation and convection to evaporation. They considered the feeling of comfort a function of the mean skin temperature. Wilkins, Newman and Doupe (146) determined local sweating response with faradic stimulation. They obtained a response over an area of $3 - 5 \text{ cm}^2$ around the needle.

This response was most easily elicited when the subject was on the verge of sweating, but it could be obtained even when the subject was shivering with cold. Local differences of sweating corresponded to the number of sweat glands. Procaine locally or denervation prevented the response to faradic stimulation but not the sweating response to Mecholyl. Block anesthesia had no effect on the response and prostigmine increased it. Issekutz and coworkers (78) also found that sweating due to pilocarpine or local heat was not inhibited by procaine or tetra-ethyl-ammonium-chloride. Nicotine sweating was inhibited by procaine and was therefore considered as an axon reflex response. Peiss (106) found that local insensible perspiration corresponds to blood flow in the particular region. Coon and Rothman (30,31) found in opposition to some of the above findings that acetylcholine induced sweating can be prevented by procaine infiltration but not by conduction anesthesia. They believe that acetylcholine causes a direct muscarinic response and an indirect nicotinic response, while nicotine effects only the postganglionic sympathetic reflex arc. Randall (116) determined local differences of sweating and their relationship to differences of blood flow. Burn (21) made similar studies on the relationship of blood flow and sweating, but instead of environmental temperature, he used pilocarpine as the stimulus.

Winslow, Herrington and Gagge (48,49,50,147,148,149,150) studied the heat exchange between the subject and his environment. They found that sweat secretion starts at an environmental temperature of 32° C and effectively prevents any further rise of skin temperature. Humidity does not influence skin temperature below 25° C and above this level skin temperature decreases progressively with increasing environmental humidity. The upper limit of homeostasis for the clothed body is with the environment

at 52° C with low humidity, and 35° C with high humidity. Sweat is regulated by the demand for dissipation of metabolic heat when other means like radiation, conduction and convection are insufficient. Increased sweat secretion with high humidity is accompanied by increased cutaneous blood flow with no change of body temperature and only slight change of skin temperature. Each major region of the body shows a critical temperature of its own, at which active sweat secretion sets in. Sharp acceleration in evaporative cooling appears in every case when the skin of the head exceeds 35.5° C, when the skin of the trunk and upper extremities exceeds 33.5° C, when the skin of the lower extremities exceeds 34.5° C. Randall (113) produced sweating by local radiation heat. For an area of 10 - 20 mm² he found a skin temperature of 39 - 45° C to be critical when applied for time period of 1 - 8 minutes. He also determined differences of response over various regions of the body and found that they essentially correspond to blood flow (111). He could not observe any seasonal changes of this response. Gurney and Bunnell (56) showed that sympathetic denervation of sweat glands does not produce histological changes of the glands and no change of their response to Mecholyll or local hot pad stimulation. After brachial block, local heating caused more than the normal response. Sufficient heating of the denervated area caused a central sweating response. In a number of publications by many authors it has been shown that sympathetic denervation prevents central sweating response in the denervated area, and that this can actually be used to outline the area of denervation (Roth, 120; Palumbo, 105; Janowitz, 80; Randall, 115; Simerone, 126). Forster and Ferguson (46) planted thermistors in the hypothalamus of cats and concluded from their

results that panting was centrally controlled and the vasomotor component of thermal regulation were reflex controlled. A comprehensive review of sweating was given by List in 1948 (96).

C. Experimental Study

a) The mechanism of heat transfer

Two types of heat transfer are used in these experiments: heat transfer by conduction and by radiation. The physical characteristics for these two methods are different, and they have to be discussed separately. This discussion is based on the sources given in the review of literature.

Heat can be transferred by conduction only if the source of the heat energy and the body which is to receive the heat are in direct contact. The amount of heat transferred depends on the temperature difference between the heat donor and the heat receiver. The heat will flow until thermal equilibrium is established; therefore heat transfer depends on the conductivity constant of the two bodies, on the temperature difference, and on the area of contact. If the body to be heated has considerable extension, the local increase of temperature depends not only on the factors mentioned but also on the point to point distribution of the transferred heat, i.e. the spread of heat in the receiving body.

The gradient (G) between two points depends on the temperature difference ($t_1 - t_2$) between the heat donor and the heat receiver and their thickness (s). Therefore
$$G = \frac{t_1 - t_2}{s}$$

If the contact area is A and the thermal conduction constant K, and the rate of heat transfer q. Then $q = K G A$

If the temperature is measured in degrees centigrade and the area in square centimeters, the conductivity in calories per second per degree centigrade per square centimeter, then the heat transfer is expressed in calories per second. The constant K is determined by the relation $K = kpc$

k = heat conductivity in calories / cm² / second / degree C

p = density per cm³

c = specific heat in calories / gram / ° C

pc is a constant which Hensel (67) determined for the human skin as 0.8

k varies for various areas of the body. Buettner (19) determined it

for the forearm as 0.0016 cal. / cm² / ° C

for the trunk 0.0013 cal. / cm² / ° C

for the finger 0.0029 cal. / cm² / ° C

kpc is largely independent of blood flow and wetting of the skin, but it varies with the layer of the skin. Hensel (68) gives the following figures:

Table 1a

Layer (mm)	kpc	Layer (mm)	k 1,2
0 - 0.26	0.0004	0 - 0.26	0.0003
0 - 0.45	0.0006	0.26 - 0.45	0.0015
0 - 0.90	0.0010	0.45 - 0.90	0.0024
0 - 1.30	0.0013	0.90 - 1.30	0.0032

For instantaneous transfer

$$G = \frac{dt}{dx}$$

$$q = \frac{dQ}{d\theta}$$

Here dt is the differential time

dx is the differential thickness

dQ is the amount of heat flowing in the differential time $d\theta$

$$\text{Then } \frac{dQ}{d\theta} = K A \frac{dt}{dx}$$

If a steady state is reached, the temperature at any given point is

independent of time. Then $q = \frac{dQ}{d\theta}$ or $q = \frac{dt}{dx} \cdot K \cdot A$

If heat is transferred by radiation, we deal with an entirely different process. Radiation is the propagation of heat energy through space. According to the Stefan Boltzman law the heat energy radiated increases with the 4th power of the temperature of the radiating source. If a body is exposed to radiation the heat energy received changes with the inverse square of the distance between this body and the radiation source. Hence

$$E = \frac{T^4 \cdot k}{d^2}$$

Where E = heat energy in calories per second

T = temperature in degrees K

k = a constant = 1.355×10^{-12}

d = distance from the heat source to the target in cm.

The biological effects of radiation depend on the wave length of the absorbed radiation. In the ultraviolet range the main effects are of a chemical nature and in the infra-red range they are of a thermal nature. Therefore increased heat of radiation is usually connected with a shift of the spectrum towards shorter wave length. This relationship

has been quantitatively expressed in Wien's displacement law:

$$\lambda_m = \frac{0.2897}{T}$$

Here λ_m is the maximal wave length and T the absolute temperature.

The discussion so far was only concerned with the heat energy that will hit the surface of the target, but it neglected the fact that we are not dealing with a two-dimensional, but to make things still more complicated it consists of many layers which differ markedly in their physical characteristics. Under these conditions the mathematico-physical approach has to be supplemented by experimental procedures. This was done by Bachem and Reed (3) who in a series of careful experiments determined for each skin layer the amount of heat reflected, the amount transmitted and the amount absorbed. From their data the following table was constructed.

Table 1b

Percentage heat absorption in the skin according to Bachem and Reed (3)

	Extreme U.V.	U.V.	Visible	Near I.R.	I.R.	Depth in mm
Wave length (μ)	0.2	0.3	0.55	1.0	10.0	
Strat. Corn.	100	66	13	29	100	0.3
Str. Malpighi		18	10	6		0.5
Corium		16	72	48		2.0
Subcut. layer			5	17		2.5

This table shows that absorption can be affected by the wave length, the physical characteristics of the various layers, and the thickness of the layers. The values given are average and neglect individual

differences, the effects of cutaneous site, of age, of the state of nutrition, of blood flow, skin colour, perspiration and probably a number of other factors.

Wolff and Hardy maintained originally that the human skin behaves, toward thermal radiation, like a perfect black body and absorbs all incident rays. Later they found that this applies only to the near infra-red range and then they used india ink in their radiation experiments to assure maximum absorption. In order to test this point, we conducted the following experiment. Ten subjects were specifically trained for accurate perception of the pain threshold. In these subjects the time of reaching this threshold with and without india ink painted on their skin was determined. Three different energy levels were used.

Table 2

The effect of india ink on thermal absorption of the skin (10 subjects).

Heat energy dial setting of milliammeter	Time to reach pain threshold in seconds	
	Without india ink	With india ink
6	25.1	4.6
7	18.6	3.3
8	15.7	2.9

This table shows that the time of reaching the pain threshold was reduced by 80 per cent when the skin was painted with india ink. Two factors combine to achieve this result. Without india ink 30 per cent of the heat is reflected (Newburgh, 101), and with india ink all is absorbed. In addition there is a change of the nature of heat transmission into the the skin. As india ink prevents penetration of heat rays into the deeper skin layers, all the incident radiant heat is absorbed by the india ink

and then transferred into the skin by conduction. Therefore the temperature gradient across the skin is that of conduction heat (graph 4) and not that of radiation heat (graph 5).

In these two graphs the time-temperature curves of the epidermal and subcutaneous temperatures were determined for various levels of energy input (numbered according to dial setting). Each point represents the mean of five determinations. For conduction heat the epidermal temperature was taken from the temperature meter of the instrument, and the subcutaneous temperature was determined by needle thermocouples, connected to a Brown potentiometer. For the radiation heat, the epidermal temperature was determined by thermocouples stretched across the field with a pressure sufficient to slightly imbed them into the skin. Registration of the temperature was by the Brown potentiometer, and the subcutaneous temperature registration was the same as that for conduction heat. In both graphs the coordination of time, epidermal and subcutaneous temperatures was obtained by means of rapid sequential photographic registration. Similarly graph 6 gives the epidermal and subcutaneous temperatures when a constant temperature is applied (details under methods).

These curves show that for conduction heat the temperature gradient across the skin is greatly increased over that of radiation heat.

Subsequently the relationships of time, temperature and subcutaneous temperature are based on these tables, and no mathematico-physical calculations are used for any of the data to be given.

This experimental approach was considered advisable as the review of the literature indicated that the attempt to mathematically analyse the physiology of sensory perception (Hardy, Buettner, Henriques and Moritz) lead to contradictory interpretations.

b) Methods of investigation

1) The heater thermometer assembly

Model A

It is felt that a detailed description of the apparatus used for the application of conduction heat is indicated because the apparatus is new and has already proved, we feel, to be valuable for various phases of physiological research.

The device is an improved form of a heater-thermometer assembly which is particularly adapted to produce a known and controlled temperature, above ambient temperature. It is installed at the end of a small probe and used to apply heat at a known temperature to a small area of the human skin. As compared with other devices used for this purpose it has the advantage of simplicity, ruggedness and compactness, its temperature may be changed rapidly, it always indicates the true temperature of the heater, and it supplies sufficient energy to actuate a rugged direct-reading temperature indicator.

The original design (Figure 1) comprises a small electric heating element of fine nichrome wire and a temperature sensing element, which is either a thermocouple or an electric resistance thermometer. If a thermocouple is used it must necessarily be made of fine wire because of the size and the heat capacity limitations of the assembly. It will therefore require a sensitive indicating meter. A multi-junction thermopile would be preferable, but would be difficult to construct in a small space. In addition, a small heater assembly of low heat capacity in contact with a body of lower temperature will not be even approximately in thermal equilibrium, and it is therefore uncertain whether the thermocouple indicates the true temperature of the heater. Similar considerations apply to the use of a resistance thermometer.

It is possible to achieve greater simplicity and at the same time assure that the indicated temperature is actually the true heater temperature by using a single small winding of electric resistance wire both as heater and resistance thermometer. This may be done by making this winding of a metal, such as nickel, which has a high temperature coefficient of resistance. This winding is used as one arm of a Wheatstone bridge circuit, the opposite arm being an adjustable calibrated resistor whose value is adjusted to be equal to that of the heater-thermometer winding at any given temperature. Thus the bridge circuit is always in a balanced condition when the temperature of the heater is determined. When this so-called "null" method is used the balance of the bridge is independent of the current supplied to it. This fact makes it possible to use the same winding both as thermometer and heater, for the heater temperature may be varied by varying the bridge supply current without affecting the temperature measurement.

This "null" method is however not well adapted to situations in which the rapid variations in temperature must be followed. In these cases a direct reading technique is preferable or essential. However when using a bridge in the "deflection" method, the readings of the meter, which in this case should be a direct indication of the temperature, varies directly with the bridge supply current. Therefore one is faced with two antagonistic requirements: (1) To maintain constant calibration, the bridge current must be kept strictly constant, and (2) To vary the temperature of the heater, the bridge current must be varied.

In the present device this dual requirement is met by passing two currents simultaneously through the heater-thermometer winding, a constant direct current for indicating the temperature and a variable alternating current to vary the temperature. The circuit is so arranged

that very little d.c. passes through the a.c. circuit and vice versa, and the d.c. indicating meter is not affected by changes in the alternating current. This circuit is shown in figure 1. The d.c. bridge consists of resistors R_1 and R_2 , the heater coil and the balancing resistor R_0 , wound of low temperature coefficient alloy. R_1 and R_2 are also of low temperature coefficient alloy and may be of equal resistance. H is of a high temperature coefficient metal or alloy, and R_0 is adjusted to be equal in resistance to the resistance of H at the lowest temperature T_0 of the desired temperature scale indicated on the d.c. bridge meter. The bridge is fed from any convenient d.c. source, and the current may be standardized by any convenient method, for example, by switching a calibrating resistor R_5 in place of H and varying the rheostat R_6 until the meter gives a standard deflection.

The a.c. bridge consists of resistors R_4 and R_5 , which may also be equal, together with H and R_0 . It is actuated by a suitable a.c. source such as a variable voltage transformer V and a step down transformer T . Heating current is passed through both H and R_0 in order to minimize the a.c. applied to the meter. In addition, the ratio of R_3 to R_4 may be varied so as to balance the a.c. bridge approximately at the maximum working value of a.c. (If necessary a choke could be connected in series with the meter to suppress the a.c. through it).

In use the heater is placed in position, switch S_1 is thrown to R_5 , S_2 is closed and R_6 varied until the meter shows a standard deflection. S_1 is thrown to H , S_3 is closed, and V is adjusted until the desired temperature is indicated on the meter. Any variation in the temperature of H is immediately shown on the meter and may be compensated by adjusting V .

It is believed that this design is superior in simplicity of construction, stability, ruggedness, and convenience to the alternatives discussed above.

Model B

In addition to the model already described (model A) in which both a direct current and an alternating current are passed simultaneously through the same electrical resistance winding, a battery operated model has been produced which operates on d.c. only (Figure 2). In this instrument the small heating element contains a bifilar winding, two very fine wires wound simultaneously and parallel to each other on a small flat rectangular form of thin sheet metal. One of these wires, made of low temperature coefficient alloy (such as nichrome), acts as the heater, while the other, which is made of high temperature coefficient material (such as nickel), is a resistance thermometer. Thus both the source of heat and the temperature sensing element are in effect distributed continuously and uniformly over the surface of the heating element. As in the model already described, this construction results in a very small, light element having a very low heat capacity and affording a very reliable indication of its temperature.

The circuit for this model is the conventional direct indicating bridge circuit, the only novelty being in the construction of the heating element as described above. The circuit is shown in figure 2 in which R_1 and R_2 are two, preferably equal, resistors, and R_3 is a balancing resistor equal in value to the resistance of the thermometer winding T when it is at the low end of the temperature range of the instrument. At this temperature the bridge is balanced and the meter M_1 , which may be calibrated directly in temperature units, shows no deflection. The

bridge current, supplied by battery E_1 , is indicated on M_3 and adjusted to its proper constant value by the rheostat R_4 . The current for the heater winding H (here shown separately but actually wound side by side with T as explained above) which is supplied by battery E_2 , is indicated on M_2 and controlled by R_5 .

In use, the switch S_1 is closed and the bridge current is adjusted to the value, indicated on M_3 , at which M_1 was calibrated. (Part of this current flows through T and heats the element slightly, well below the lowest temperature needed in actual use). S_2 is then closed and the current through H is varied to obtain the desired temperature as shown on M_1 . The heat output may be found from the current shown on M_2 and the known constant resistance H.

While the measurements obtained with the instrument are essentially restricted to this particular method, it is attempted to give as much objective information as possible. Therefore the three meters used in the instrument have been measured.

The standard meter (M_1) has a scale from 0 to 10 and a full deflection value of 47 milliamperes. To balance the instrument the meter setting is at 8 which corresponds to 37.6 milliamperes.

The energy meter (M_3) has a scale from 0 to 100 and a full deflection value of 144 milliamperes.

The temperature meter (M_2) has a scale from 0 to 100 and a full deflection value of 7 millivolts.

Subsequently figures given as meter readings are with reference to these values. As the instruments are hand-made, they apply to one instrument only. Absolute values for any determination and comparison between different instruments can be made on the basis of these data.

In this investigation meter readings are given to indicate variability and to make it possible to compare methods and effects; objective values are given when they are considered to be of physiological interest.

Figure 3 shows the applicator upside down to bring out the small square area which is placed in contact with the skin. The weight of the applicator is 28 grams, and is supported by three legs. If additional weight is desired, it can be attached, as shown in figure 3, below the tip.

2) Methods of application of heating Instrument

There are several ways in which the apparatus may be used.

1. The temperature of the applicator might be raised to the desired temperature before application, and later applied to the skin and its temperature maintained regardless of the energy required to hold the applicator at the fixed temperature when in contact with the skin. This method was found unsuitable, as on application to the skin there is a marked fall of the temperature of the applicator which could not be accurately compensated. Consequently variations resulted as it takes several seconds for a steady temperature to be obtained.

2. The energy supplied to the applicator may be fixed and maintained after applying the applicator to the skin without regard to its temperature. This method proved very reliable in all cases where the energy was not changed and time or temperature, or both, were used as variables. In this series it was used for the determination of sensory thresholds.

3. The temperature of the applicator after applying it to the skin might be raised to a desired level within a fixed period of time and then maintained stationary at that level independent of the energy necessary to do this. This method was found suitable for experiments with

fixed temperature and fixed time. It was used for determination of injury threshold and for production of standard injuries, to determine the influence of locality, of environment and of drugs. By determining the energy needed to obtain and maintain a given temperature it was possible to determine which factors prevent or enhance injury production and which factors affect healing.

3) Calibration methods

The construction of the probe as described above brings the heater and thermometer windings into very close thermal contact with the probe surface. However, since these windings must necessarily be insulated electrically, there will be a temperature difference between the thermometer element and the probe surface, and this difference will vary when the heat flow from the probe is varied. This was done by inserting the probe in a rapidly stirred thermostable water bath without any heater current flowing. Then the same temperature was obtained by means of the heater current and the surface temperature of the applicator was determined by means of thermocouples. The resulting temperature variations were from 0.2° C to 0.4° C over the usual range of heater current. Since this differential is constant for any given current value, appropriate small corrections were made on the calibration curve of the instrument.

Several methods of calibration were tried, and the following procedure was adopted because it is convenient and gives accurately reproducible results.

Into the side wall of the water bath an aluminum rod, $5/16$ inch diameter by 3 inches long, is fixed with its outer end flush with the wall and its inner end projecting into the water. The outer end of the rod is

machined accurately flat. A collar of phenolic insulates the rod thermally from the wall so that its outer end is substantially at the same temperature as the water within the bath. The end of the probe is held in close contact with the outer end of the rod by a spring clamp with a light coating of petroleum jelly between the surfaces to insure good and constant contact. There is no detectable difference between the temperature taken at the end of the rod and with the probe immersed in water. (This method precludes the possibility of moisture penetrating into the probe.)

With the bridge supply current maintained at a proper predetermined value, and with the heater current at zero, the water temperature is varied in steps of 3 to 4° C and readings are taken of the water temperature, with a 0.1° C precision thermometer, and at the same time of the deflection of the bridge meter. (As explained above, the low end of the temperature scale on this meter may be adjusted to any desired value by adjusting the value of the resistor R_3 . The range of the meter, in degrees, may be varied by changing the bridge current as shown on meter M_3 . Increasing the current increases the sensitivity of the bridge, that is, it reduces the range of the meter. In a typical case, with the thermometer resistance of 7.35 ohms at 40° C, and a bridge current of 282 milliamperes, the scale range was 36 to 56° C.)

In this case the power dissipation of the thermometer winding at the low end of the scales is 0.035 gram calories per second, and it increases slightly at higher temperatures. The heater winding, resistance 41.1 ohms, provides heat dissipations* from zero to a maximum of 0.10 gram

*Calculated by the formula: $H = 0.239 i^2 R$

H in gm cal/sec

i in amperes

R in ohms

calories per second, at a current of 100 milliamperes.

The total temperature range is from 38° C to 66° C. Therefore each unit on the temperature meter corresponds to a temperature change of 0.28° C. These values may change somewhat from one applicator to another and from one instrument to another.

4) Radiation heat

With the above described instrument heat was transmitted by conduction only. As radiant heat has been used in the traditional methods, especially in pain determination, it was considered desirable to obtain comparative values for radiation heat and for conduction heat. For this purpose a tungsten filament light bulb was used as heat source. A series of lenses focussed the beam, at a distance of 3 inches, on an area of approximately the same size as that of the probe (5 x 5 mm). A rheostat was used to vary the energy input. The wave length of the instrument according to information obtained from the manufacturer spreads over a range of 5,000 to 15,000 angstroms with a peak at about 10,000 angstroms. Skin temperature was measured with thermocouples consisting of a constantan and a steel wire each five thousandths of an inch in diameter. The two wires were soldered end to end and stretched across the field with the recording point in the center. For registration they were connected to a self-balancing Brown potentiometer. It was realized that the values obtained are not true temperature values due to the effect of direct heat rays on the thermocouples; however, no better method was available, and for comparative purposes the method was considered adequate.

5) Subcutaneous temperature determination

For the determination of subcutaneous temperatures special needle thermocouples were constructed. A round steel wire, five thousandths of an inch in diameter was filed half round for a length of three inches. A constantan wire of the same diameter was treated similarly. Both wires were insulated and baked together while the tips were soldered and sharpened to form a needle thermocouple ten thousandths of an inch in diameter. The thermocouple was connected to a self-balancing Brown potentiometer. The various factors of surface temperature, subcutaneous temperature, time, and heat energy were coordinated by rapid sequential photographic registration. When two thermocouples were used at different skin depths, a switch was interpolated so that one temperature was shown on all even numbered photographs and the other on all uneven numbered photographs.

The readings of subcutaneous temperature and the changes which occur on the application of conduction heat to the skin surface should give a fairly reliable indication of the actual skin temperature. However, the actual meaning of any thermocouple temperature measurement with radiation heat is very doubtful. If the electrode is placed at a tissue depth of 1 mm we have to assume that 50 per cent of the incident rays are absorbed before they reach this tissue depth. The thermocouple fully stops the remaining 50 per cent which is normally only absorbed at greater depth. Even if there is a tendency to equalize the temperature of the needle to that of the surrounding tissues, there is no doubt but that the needle still indicates a higher temperature than the tissue temperature in the absence of the thermocouple. This error is probably unavoidable. No attempt is made to correct for this; but instead the values are considered only as comparative and not as true temperature measurements.

Pain threshold determinations are impossible with a subcutaneous needle in place because of the irritation due to the needle. Similarly for injury production the presence of a subcutaneous thermocouple may be a complicating factor. Therefore it was decided to make separate determinations of the relationship of the epidermal to the subcutaneous temperatures over the whole range of experimentation using the various methods. This was done in 10 subjects and the mean values obtained are given in figures 3, 4 and 5. Subsequently most subcutaneous temperatures were determined by referring to these graphs. However, if environmental conditions were changed, or if drugs were used which influence the blood flow, new determinations of the subcutaneous temperatures were made under the particular conditions

6) Subjects

Human subjects were used in all experiments, some were medical and graduate students and some were hospital patients.

7) Reliability tests.

To determine the reliability of the instrument and of the method, pain threshold and flare threshold were determined on nine clinical patients four time in one day (Table 3) and later, using the same patients, once a day for ten days (Table 4).

The results show that the measurements are adequate for skin flare measurements but not for pain. It was concluded that pain measurements are not possible under clinical conditions and that the effect of age and sex must be controlled. Therefore a group of young men were specifically trained for accurate perception of pain. Using a constant energy for flare and pain production, their thresholds were determined.

Table 3

Variation of the thresholds of skin flare and of pain during one day.

(Units are meter readings.)

<u>Diagnosis</u>	<u>Sex</u>	<u>Age</u>	<u>Flare threshold</u>				<u>Pain threshold</u>			
			<u>Time of Day</u>							
			<u>8:00</u>	<u>12:00</u>	<u>4:00</u>	<u>8:00</u>	<u>8:00</u>	<u>12:00</u>	<u>4:00</u>	<u>8:00</u>
Cellulitis	M	37	52	52	52	52	66	73	62	61
Infected burn	M	34	48	48	46	48	50	59	56	61
Frostbite	M	44	48	48	48	48	71	75	71	66
Cancer of oesophagus	M	50	58	58	58	58	54	53	53	46
Stasis, leg ulcer	M	59	50	48	48	48	65	61	65	58
Rheumatic heart disease	F	54	52	50	50	50	56	50	60	56
Rheumatic heart disease	F	26	48	48	48	48	47	49	58	54
Recent C.V.A.	F	79	56	56	56	56	57	64	59	56
Coronary occlusion	F	66	52	50	52	52	70	65	66	70

Table 4

Variations of the thresholds of skin flare
and of pain during 10 consecutive days

(Units are meter readings.)

<u>Diagnosis</u>	<u>Sex</u>	<u>Age</u>	<u>Flare threshold</u>		<u>Pain threshold</u>	
			<u>Flare Threshold</u>	<u>No. of days</u>	<u>Threshold mean</u>	<u>Standard error</u>
Cellulitis	M	37	52	10	66	1.63
Infected burn	M	34	48	3	55	1.41
			50	7		
Frostbite	M	44	48	9	65	1.93
			50	1		
Cancer oesophagus	M	50	56	6	57	2.74
			58	4		
Stasis, leg ulcer	M	59	50	7	59	2.03
			52	3		
Rheumatic heart disease	F	54	50	6	57	1.42
			52	4		
Rheumatic heart disease	F	26	48	8	49	1.29
			50	2		
Recent C.V.A.	F	79	54	2	61	2.31
			56	8		
Coronary occlusion	F	66	50	5	64	2.11
			52	5		

The results show good agreement of the pain threshold and of the flare threshold and a fairly constant ratio between these two reactions (Table 5).

After this preliminary investigation it was considered possible to use this method, not only to determine each single reaction, but also to obtain comparative data for the relationship between various objective and subjective responses.

c) The sensations produced by local heat application

1) The pain sensation

For the determination of the pain threshold a constant energy input was used. The applicator was placed on the skin and the temperature was increased with a constant energy input. The threshold was taken as the point where pain was first reported. This point was recorded in time and temperature units.

In the first series of experiments the influence of the level of energy input, which determined the rate of temperature rise, on the pain threshold was studied. The subjects, as mentioned, were specifically trained for accurate perception of the pain threshold. By changing the rate of temperature increase in a random fashion the element of subjectivity was largely eliminated.

The results (Table 6) show that the thresholds in terms of surface temperature are directly related to the energy input. Since the rate of temperature change is directly related to the energy input, these data also show that the surface temperature, at the time the pain threshold is reached, is directly related to the rate of increase of temperature. There is an inverse relationship of time required to reach the pain threshold and of the temperature at the time pain is perceived. Figure 8 illustrates

Table 5

The thresholds of pain and skin flare in trained subjects.
(Units are meter readings)

<u>No.</u>	<u>Pain threshold</u>	<u>Flare threshold</u>	<u>Ratio</u>
1	57.5	65	1.13
2	60	70	1.17
3	62.5	70	1.12
4	66	75	1.14
5	57.5	67.5	1.17
6	62.5	75	1.12
7	56	65	1.16
8	60	70	1.17
9	62.5	72.5	1.16
10	65	72.5	1.12
11	70	75	1.07
12	62.5	72.5	1.16
13	72.5	80	1.10
14	70	80	1.14
Mean	63.2	72.1	1.14
s.e.	1.3	0.8	0.03

Table 6

The effect of various heat energy inputs on the threshold of heat pain. The values are the means obtained on five determinations in each of ten subjects. The standard errors of the means are given.

<u>Energy</u>	<u>Threshold time</u>		<u>Surface temperature</u>		<u>Subcutaneous temperature</u>	
	<u>Seconds</u>	<u>s.e.</u>	<u>°C</u>	<u>s.e.</u>	<u>°C</u>	<u>s.e.</u>
25	52	3.21	45.2	0.41	40.4	0.63
30	17	0.93	49.4	0.49	39.8	0.52
35	10	0.27	51.9	0.63	40.8	0.42
40	8.5	0.17	53.3	0.97	40.3	0.69
45	7.0	0.10	54.0	0.81	41.0	1.02

this relationship, and figure 9 shows that by plotting the surface temperature at pain threshold against the time at threshold a typical strength-duration curve is obtained.

These findings are confirmed by the following simple experiment. If the hand is immersed in lukewarm water and the water is slowly heated, the pain threshold is 43° C. However, if a series of basins of water at various temperatures are tested to see which one produces an immediate sensation of pain on immersion, the threshold is found to be 47° C.

The results suggest also that heat pain is not a function of the temperature gradient of the skin, as suggested by Wolff and Hardy group. If we look at the subcutaneous temperatures we find that in each case the temperature was approximately 40° C independent of energy and time factors. (Table 6) This relationship is diagrammatically represented in figure 7 which plots two different energy levels with P indicating the pain threshold. Before drawing conclusions from these findings it was considered advisable to do some additional control studies.

In those of our experiments in which the pain threshold is reached within a few seconds, it was thought possible that the time for impulse conduction, central registration and realization may influence the experimental results. To determine the influence of these factors an energy of 45.0 units was used, but the energy in this series was cut down after five seconds when a temperature of 52.0° C was reached and the temperature held at that level until pain was perceived. In all experiments pain occurred at about ten seconds after beginning the heat application (mean of ten experiments 9.3 seconds). The time was always more than seven seconds. Using an energy of 45 units with uninterrupted temperature rise the pain threshold is reached after seven seconds when

a surface temperature of 54.0° C is reached. Table 6 shows the time at 52° C to be about ten seconds, and as we found 9.3 seconds as the mean, we consider this experimental result as an indication that the various factors of conduction and reaction time are not significant in these determinations.

The results raise the question of the physiological mechanism involved in the pain sensation. Various authors have attributed the stimulus for heat pain to be dependent upon the following factors:

- 1) The absolute temperature applied;
- 2) The rise of temperature above a physiological zero level;
- 3) The rate of temperature change;
- 4) The temperature gradient across the skin;
- and 5) The temperature difference between adjoining cutaneous regions.

While the findings in this series do not definitely prove or disprove any of these theories, the simplest and most obvious explanation is Buettner's concept of an absolute temperature threshold at a point somewhat below the skin surface. Buettner arrives at this conclusion on the basis of theoretical calculations and this may be the cause of some differences between his results and those of this investigation. A discussion of this seems necessary. He places the receptor point at a depth of 0.1 mm while the findings presented here indicate a depth of about 1.0 mm. Histological and physiological evidence (15,16,141,153) support a reception in the deeper epidermal layers at a depth of 1 mm or perhaps slightly less. While 0.1 mm may be too superficial it cannot be maintained that the experiments reported here allow conclusion on the exact location of the depth of reception. The selected depth of 1.0 mm was only approximate and exact depth determinations with thermocouples is practically

impossible. If the arbitrary depth of 1.0 mm yielded a good correlation this does not exclude the possibility that at other levels an equally good or even better correlation may be obtained.

There is a marked difference in the absolute threshold temperature given by Buettner and the one given here. Buettner considered the threshold to be at 44.8° C, while this writer found 40° C as the approximate subcutaneous threshold. It is felt that this is due to the different depth of determination and of methods. As explained before, thermocouples in the field of radiation are likely to yield values several degrees higher than the true tissue temperature. It is therefore felt that the values obtained in the described experiments are probably nearer to the true tissue temperature at the receptor level.

2) The heat sensation.

While it is comparatively easy to train subjects for accurate perception of the pain threshold, it is very difficult to obtain comparative values for the sensation of heat. This is surprising because a difference of temperature of only 0.2° C can be definitely perceived. However, when the temperature changed gradually, threshold determination becomes more difficult. Wolff and Hardy are, according to the writer's knowledge, the only group who succeeded in the determination of a definite threshold for heat sensation. They express their threshold in energy units and find that it is 1/1900 th. of the energy necessary to produce the pain threshold. Using our methods this determination was tried many times in a great number of subjects; environmental conditions were fixed and all possible distracting factors eliminated; conduction heat and radiation heat were used, but the results were consistently negative. Usually slight fluctuations of some vague temperature sensation are noticed,

gradually becoming more pronounced; however, when the subject is asked to determine a definite threshold, the threshold may vary anywhere between skin temperature and the pain threshold, without correlation with any known factor. This negative result is in itself interesting because it indicates that it is not possible to determine the threshold or intensity of heat by use of such small skin areas. Hensel (67,68,69) with his much more refined methods arrived at his three-dimensional concept of heat perception, which is discussed in the review of the literature, and to which nothing can be added by the approach used in this investigation.

d) The reactions to heat injury

1) The threshold of the various reactions

It is the purpose of this part of the investigation to determine the time and temperature factors in the production of 1) skin flare (axon reflex), 2) macule (local red spot), 3) blister. The ten subjects for these experiments were males between the ages of 20 to 38 years. The lesions were produced at the upper part of the back. The applicator was placed on the skin and the temperature raised to the desired level within 15 seconds. The temperature was then held constant for the time indicated. The reactions were observed for five minutes following the heating period. The area was inspected again after four hours and after 24 hours. In every subject at least four different temperatures at 1.0° C intervals and at three different lengths of time of application (0.5, 1 and 2 minutes) at each temperature were used for each type of injury reaction. Several subjects were studied repeatedly and gave essentially identical reactions each time. The results are given in table 7 indicating how many of the ten subjects gave a positive response at the particular temperature and time.

From these experiments it can be seen that all of these skin reactions occur within the comparatively small range of from

Table 7

The threshold for various skin lesions produced by heat. (10 subjects)

The numbers indicate how many of the ten subjects gave a positive response.

		Skin Flare									
Temp. ° C		42.5	43.5	44.5	45.5	46.5					
1/2 min.		0	2	5	8	10					
1 min.		0	1	3	10	10					
2 min.		0	2	4	10	10					
Macule seen at 4 hours											
Temp. ° C		46.5	47.5	48.5	49.5	50.5	51.5	52.5	53.5	54.5	
1/2 min.		0	0	0	0	2	2	4	4	10	
1 min.		0	0	0	0	4	4	10	10	10	
2 min.		0	6	7	10	10	10	10	10	10	
Macule seen at 24 hours											
Temp. ° C		47.5	48.5	49.5	50.5	51.5	52.5	53.5	54.5		
1/2 min.		0	0	0	0	0	1	4	10		
1 min.		0	0	0	2	4	6	10	10		
2 min.		0	4	5	6	10	10	10	10		
Blister seen at 4 hours											
Temp. ° C		50.5	51.5	52.5	53.5	54.5	55.5	56.5	57.5		
1/2 min.		0	0	0	0	0	2	4	10		
1 min.		0	0	0	2	5	6	10	10		
2 min.		0	1	3	4	10	10	10	10		
Blister seen at 24 hours											
Temp. ° C		50.5	51.5	52.5	53.5	54.5	55.5	56.5	57.5		
1/2 min.		0	0	0	0	0	2	6	10		
1 min.		0	0	0	2	5	10	10	10		
2 min.		0	1	3	7	10	10	10	10		

43.5° to 57.5° C. This agrees with the findings of Lewis and others. The range of variability among different subjects for each type of reaction in this series is not more than 4° C.

Flare is a temporary phenomenon, which appears almost immediately and disappears in three to ten minutes. Within the limits of the time period used in these experiments the duration of heat application does not appear to be of much significance in the production of this lesion.

Macules develop more slowly and reach their maximum after four hours. They may have disappeared after 24 hours and only if a higher than threshold temperature is applied are they likely to persist for 24 hours or more. The duration of heat application appears to be a definite factor in the production of macules.

Blisters are still slower in their development and may need more than four hours. Once they are present they persist for 24 hours or more. The duration of stimulation appears to be a factor in the production of this type of injury.

2) The skin flare reaction

The review of the literature showed that skin flare is a much discussed phenomenon, and that in spite of this the mechanism of its production is still uncertain.

In the reliability tests (Tables 3 and 4) the threshold of skin flare was surprisingly steady; however, it was felt that a more careful study of various influences was necessary before any conclusions could be drawn.

In the next series of experiments the influence of environmental conditions was determined. Eight subjects were selected and the determinations of temperature threshold and energy necessary to maintain

the threshold temperature were made with room temperatures of 70° F, 33° F, and 108° F.

The results are shown in table 8. It will be noted that the threshold of flare was not influenced by the room temperature. However, the amount of energy required to maintain the temperature of the applicator tip varied directly with the external environmental temperature. This would indicate that the rate of blood flow through the skin or the temperature of the skin (within these limits) are not important factors in determining the threshold of skin flare.

Table 8

The influence of environment on the threshold and energy requirement of skin flare.
(8 subjects; units are meter readings.)

<u>Room temperature</u>	<u>Flare threshold</u>		<u>Energy</u>	
	<u>Mean</u>	<u>s.e.</u>	<u>Mean</u>	<u>s.e.</u>
70° F	53	1.0	24	1.8
33° F	53	0.9	30	2.8
108° F	53	1.2	17	1.6

It was found that immersion of the arm before the test for five minutes in either warm water (43° C) or cold water (14° C) raised the threshold. In the next series the effect of various systematically applied drugs was tested.

The results (table 9) indicate that histamine and epinephrine do not affect the threshold of skin flare as far as temperature is concerned, but they do have a marked effect on the energy necessary to obtain and maintain the threshold temperature. The effect of epinephrine is not statistically significant. However, there can be no doubt about the trend.

Table 9

The influence of systematically applied neuro- and vasoactive drugs on the threshold of skin flare.
(8 subjects; units are meter readings.)

	<u>Threshold</u>	<u>Energy</u>		<u>Size of flare</u>	
		<u>Mean</u>	<u>s.e.</u>	<u>Mean</u>	<u>s.e.</u>
Control	26	16.5	0.3	19.1	1.9
Histamine 0.01 mg/kg	26	19.2	0.4	21.6	2.1
Epinephrine 0.25 cc 1:1,000	26	16.2	0.3	19.6	1.7
Morphine 10 mg	30*	21.5	0.5	22.1	2.4

The drugs were injected in one arm and the test was made on the other arm.

*With morphine the energy required to hold the temperature at 26 was 17.9 with a standard error of 0.4.

The effect of morphine is very interesting. The vasodilatation caused by morphine probably is more a release of vasoconstrictor tonus than active vasodilatation. If this effect of morphine is an effect on the nerve and not on the chemical mediator, this may be an interesting clue to the nature of the flare reaction and the variability under physiological and pathological conditions.

As a check on these results, adrenaline and histamine were injected locally and the flare threshold determined at the site of injection. The results (Table 10) confirm the previous observations.

Table 10

The effect of intradermal injections of vasoactive drugs on the flare threshold.
(8 subjects)

<u>Substance</u>	<u>Threshold</u>	<u>Energy</u>		<u>Size of flare in mm</u>	
		<u>Mean</u>	<u>s.e.</u>	<u>Mean</u>	<u>s.e.</u>
Saline 0.1 cc	47	29	1.80	32	0.58
Adrenaline 0.1 cc 1:1,000	47	27	1.43	36	1.43
Histamine 0.1 cc 1 mg./cc	47	31	1.91	46	1.70

Antihistaminics were tried in eight subjects and it was found that Pyrabenzamine (100 mg by mouth) did not influence the threshold; a larger dose may have done so.

In the next series of experiments the influence of age on the threshold of skin flare was determined. The results (table 11) show a clear increase of the threshold up to 60 years, and then apparently a plateau is reached. This effect of age can possibly be explained by decreased heat dissipation in the aged due to increased dryness of the skin, or it may be due to decreased reactivity of the peripheral nervous

system. The first idea is supported by the increased threshold for injury in the aged and the second by the increased threshold for pain. It seems likely that both factors may combine to produce the results shown.

Table 11

The influence of age on the threshold of skin flare

<u>Decade</u>	<u>No. patients</u>	<u>Mean threshold</u>
0 - 9	1	65
10 - 19	21	71.3
20 - 29	72	74.3
30 - 39	76	75.6
40 - 49	81	77.3
50 - 59	82	77.6
60 - 69	70	78.1
70 - 79	37	78.8
80 -	14	78.2

3) The reactions to severe injury

The thresholds of the various injury reactions were given in a previous section. They were determined by varying the conditions of stimulation and holding constant other factors such as the site of stimulation, skin temperature and inferentially the blood flow. The question now is to ascertain what factors determine the nature and severity of the reaction to a stimulus of fixed temperature.

Clinically it is recognized that there are areas of the body where wounds tend to heal more rapidly than other areas. These differences have never been confirmed experimentally nor were the factors responsible for such differences determined.

Throughout these experiments conduction heat was used. Standardized lesions were produced by applying the applicator to the skin and raising the temperature to 54.5° C within 30 seconds. The temperature was held at this level for one minute, at the end of which time the applicator was removed from the skin. The injured area was inspected after 24 hours and again after 10 days, at which times recordings were made of the nature and the size of the ensuing lesions. A lesion was considered "severe" if it were more pronounced than a macule, i.e., a papule, a blister, or a crust. No protection by gauze or dressing was used as the lesions produced by this instrument are small and superficial. The 24 hour reaction was considered as "reaction to injury", the difference between the 24 hour reaction and the 10 day reaction was considered "healing", while the "10 day reaction" was considered a summation of these two factors.

In 10 subjects skin injuries were produced over various parts of the body as shown in table 12 A. After 24 hours there was no significant difference in the size of the lesions, but the number of severe lesions varied markedly in different areas. Ten days later (table 12 B) there were pronounced differences in the size of the lesions. At this time also the number of severe lesions was markedly decreased since the 24 hour observation, most noticeable so on the back. Table 12 C indicates a much higher rate of healing for the back and the calf of the leg than for any other region investigated.

In the next series four lesions were produced 4 inches apart along the side of the leg between the popliteal fossa and the ankle. This area was chosen because it shows a fairly regular decrease of skin temperature down the leg, and according to Hordon and Sheard (72) an increase of vascular tonus down the leg. Twenty subjects were used.

Table 12

A
Injury reactions after 24 hours. (10 subjects)

	Upper arm	Lower arm	Back	Abdomen	Calf of leg
Size of lesion (mm)	5.3	5.1	5.3	5.5	5.2
s.e.	0.2	0.2	0.1	0.2	0.1
No. severe lesions	8	6	8	10	2

B

Injury reactions after 10 days. (10 subjects)

	Upper arm	Lower arm	Back	Abdomen	Calf of leg
Size of lesion (mm)	4.6	4.3	3.6	5.1	3.0
s.e.	0.1	0.2	0.1	0.2	0.2
No. severe lesions	2	2	0	5	0

C

Healing in nine days. (10 subjects)

	Upper arm	Lower arm	Back	Abdomen	Calf of leg
Decrease of size of lesion (mm)	0.7	0.8	2.7	0.4	2.3
% decrease of severe lesions	75	67	100	50	100

D

Injury reactions along the leg after 24 hours. (20 subjects)

	1	2	3	4
Site of lesion				
Size of lesion (mm)	4.8	5.1	4.9	5.0
s.e.	0.3	0.1	0.2	0.2
No. severe lesions	0	2	11	5

E

Injury reactions along the leg after 10 days. (20 subjects)

	1	2	3	4
Site of lesion				
Size of lesion (mm)	2.7	3.0	4.3	4.6
s.e.	0.1	0.1	0.3	0.2
No. severe lesions	0	0	11	4

F

Leg injuries of 10 patients on bed rest. (24 hour reaction)

	1	2	3	4
Site of lesion				
Size of lesion (mm)	4.3	5.2	5.3	5.0
s.e.	0.3	0.2	0.2	0.2
No. severe lesions	0	0	2	0

G

Leg injuries of 10 patients on bed rest. (10 day reaction)

	1	2	3	4
Site of lesion				
Size of lesion (mm)	2.0	2.5	2.7	2.6
s.e.	0.2	0.2	0.2	0.2
No. severe lesions	0	0	1	0

The results (table 12 D) show that after 24 hours there was a marked difference in the size of the lesions in the various areas examined. The severity of the lesions shows a sharp peak at site three which is just below the lower end of the calf. After ten days there is a regular gradient in the size of the lesions with an increase peripherally, and site three again shows the highest incidence of severe lesions. (Table 12 E and figure 10). It is interesting that this is the site where clinically ulcers are most likely to occur.

Statistically the difference in size between the first and the second, and the third and the fourth lesions are not significant; however the difference in size of any of the upper two lesions against any of the lower two is significant. Healing also is much faster in the two upper lesions than in the two lower ones.

To determine whether a standing position may be responsible for this gradient along the leg, a similar series of tests was made on ten hospital patients who for medical reasons were confined to bed. The results (table 12 F and 12 G) show that the gradient down the leg is not nearly so pronounced as it is in those walking about. The healing rate is enhanced in bed patients.

These findings, of site on the reaction to injury, raised the question as to the factors responsible for these differences.

Movement of the skin is known to have a definite influence on healing, but the sites used here are comparatively immobile.

Skin flare, as an indication of vascular reactivity, was determined for all the sites tested and no significant change of the threshold could be obtained. The size and the intensity of skin flare are not reproducible factors, and therefore they could not be used for evaluation of local differences of injury reaction.

Various other factors that may have some relation to injury reaction and healing are given in table 13. Skin thickness was taken as the thickness of the epidermis as given in dermatological textbooks. Skin temperature was determined with skin thermometers. Circulation index as defined by Sheard (124) is the relation of skin temperature to rectal temperature. The distribution of pain points and the pain pressure thresholds were taken from Strughold (136).

The data combined into table 13 indicate that some of these factors may have some influence on injury production and healing, but the relationship is only partial and clearly needs further investigation.

Table 13

The relationship of injury reaction and healing to various physiological variables.

	<u>Upper arm</u>	<u>Lower arm</u>	<u>Back</u>	<u>Abdomen</u>	<u>Calf of leg</u>
Size of lesions after 24 hours (mm)	5.3	5.1	5.3	5.5	5.2
No. severe lesions (24 hours)	8	6	8	10	2
Healing in 9 days	0.7	0.8	2.7	0.4	2.3
% decrease of severe lesions	75	67	100	50	100
Skin thickness (mm)	1.2	1.4	2.8	1.8	2.2
Skin temperature (° C)	32.9	30.0	33.6	34.2	32.2
Circulation index (Sheard)	2.28	1.82	2.96	3.75	1.95
Pain points/cm ² (Strughold)	208	203	212	188	172
Pain pressure threshold (Strughold)	0.29	0.32	0.47	0.54	0.70

The factors which, from a physiological point of view, were considered most likely to exert an influence, are skin temperature and blood flow. Consequently these were further investigated in a series of experiments on ten bed patients.

Injuries were produced at corresponding sites of both legs. One hour later one of the legs was covered with an electric pad which was maintained for three days at a temperature of 99 to 101° F, while the other leg was left uncovered. It was found (table 14 A) that after ten days the lesions on the control side had an average diameter of 2.4 mm, while the lesion on the heated leg had an average diameter of 1.8 mm.

Cold was applied by the use of an ice bag at 45° to 65° F. The size of the lesion at the end of the experimental period was 2.6 mm. The difference of size between the heat treated lesions and the controls was significant, while the difference between the cold treated lesions and the controls was not significant.

Table 14

A

The effect of heat and cold when applied for three days starting one hour after injury. (10 bed patients)

	<u>24 hour reaction</u>		<u>10 day reaction</u>	
	<u>Size of lesion</u>	<u>No. severe lesions</u>	<u>Size of lesion</u>	<u>No. severe lesions</u>
Control	4.5 mm	2	2.4 mm	2
Cold (45° - 65° F)	4.5	2	2.6	2
Heat (99° - 101° F)	4.2	2	1.8	0

B

The effect of heat and cold when applied 10 minutes before until 1 hour after injury. (10 bed patients)

	<u>Energy (meter readings)</u>	<u>24 hour reaction</u>		<u>10 day reaction</u>	
		<u>Size of lesion</u>	<u>No. severe lesions</u>	<u>Size of lesion</u>	<u>No. severe lesions</u>
Control	25	4.6	3	2.5	2
Cold (45° - 65° F)	30	4.5	0	2.0	0
Heat (99° - 101° F)	21	4.6	6	3.4	5

To determine the influence of heat and cold on injury production, the procedure was the same as described in the preceding paragraph but this time the application was started 10 minutes before injury production and continued until 30 minutes after injury production. The results (table 14 B) show that cold increased the energy required to obtain the injurious temperature and it decreased the severity of reaction, while heat decreased the energy need and increased the severity of reaction.

In studying the influence of blood flow on the injury reaction a difference was made between the blood content of the tissues and the actual movement of the blood. Blood content of the tissues affects heat capacity and heat conductivity, while the rate of flow determines how much heat is carried away by the heated blood from the area of stimulation. To increase the blood content of the tissues experimentally venous congestion of the arm was produced with a pressure cuff at 80 mm. Hg. To decrease the blood content a relatively bloodless arm was obtained by raising the arm for one minute and then suddenly occluding it with a cuff pressure of 200 mm Hg. Injury was produced immediately after the occlusion while the cuff was still on. In both of the conditions mentioned there was no blood flow through the arm.

To increase the blood flow experimentally, a bloodless arm was obtained as described and after three minutes of obstruction the pressure was suddenly released and the injury was produced while the arm was in the deep blush of passive hyperemia (table 15).

Table 15

The effect of change in blood supply and blood flow
on injury production. (10 subjects)

	24 hour reaction			10 day reaction	
	<u>Energy meter reading</u>	<u>Size of lesion</u>	<u>No. severe lesions</u>	<u>Size of lesion</u>	<u>No. severe lesions</u>
Control	25	4.6	6	3.6	5
Venous congestion	23	4.5	5	3.4	5
Bloodless	22	4.5	5	3.1	4
Passive hyperemia	28	4.5	5	3.7	5
Epinephrine	24	4.5	4	3.3	2
Histamine	33	4.7	6	3.8	6

As a more physiological approach a relatively low blood content plus low blood flow was obtained by the systemic application of 0.25 cc of epinephrine 1:1,000 and of histamine 0.01 mg/kg body weight. The results (table 15) indicate that blood content of the tissues might have a slight effect on the injury reaction, but in this series it is not significant. The energy required to maintain the injurious temperature is little affected by the blood content of the tissues. However, the influence of blood flow is very marked. With decreased flow the severity of lesions is greatly decreased and the requirement of heat energy is lowered. With increased blood flow there is a tendency towards increased severity of injury reaction, which is not significant in this series, but a larger series of tests might make it definite. The increase of heat energy with increased blood flow is statistically significant.

In these experiments standard lesions were produced by the application of a fixed temperature independent of the energy necessary to obtain or maintain this temperature. If a fixed heat energy had been used

instead of a fixed temperature, everything in these experiments that shows change of the heat energy (first column, table 15) would add to or subtract from the observed injurious effect.

The data show also that the changes in blood supply and blood flow do not have nearly as much effect on injury production as changes of temperature. This may be an indication that under the conditions of these experiments the effects of blood flow on injury production are really temperature effects.

e) The sweating reaction

As Randall (113) had demonstrated, local sweating can be produced by local heat application. In the following section it is attempted to determine the threshold of this reaction, the various factors influencing it, and its possible physiological significance.

In these tests conduction heat was used. The site of testing was the inside of the forearm and the subjects were medical and graduate students.

All tests were made on the inside of the forearm.

The area to be tested was painted with tincture of iodine, the heat was applied and immediately afterwards the response or non-response was determined by the application of starch paper under light and even pressure. The discoloration or non-discoloration showed whether or not there was a response. For threshold determination this procedure was repeated until two measurements with a difference of not more than 0.4°C gave a positive and a negative response respectively. The tests were made under controlled environmental conditions (Figures 17, 18). In the first series of experiments the environmental conditions were kept constant at a temperature of 82°F and 65% relative humidity. The relation of the

duration of heating to the threshold of sweating was determined. Using ten subjects it was found that the mean threshold was 38.3° C for a three minute heating period; 41.4° C for a two minute period; and 46.0° C for a one minute period.

In a second series of tests the time of heating was kept constant at three minutes and the influence of changes in environmental temperature and humidity was determined.

Table 16

The influence of environmental conditions on the skin temperature and the sweating threshold. (7 subjects)

<u>Environmental Temperature</u>	<u>Relative Humidity</u>	<u>Subcutaneous Temperature</u>	<u>Epidermal Temperature</u>	<u>At Sweating Threshold</u>	
				<u>Subcutaneous Temperature</u>	<u>Epidermal Temperature</u>
$^{\circ}$ F	%	$^{\circ}$ C	$^{\circ}$ C	$^{\circ}$ C	$^{\circ}$ C
60	75	31.6	31.8	39.9	46.4
60	21	29.4	29.4	41.2	48.1
65	85	31.9	32.2	40.1	46.5
65	17	31.0	31.9	40.9	48.8
70	90	32.5	32.7	39.8	46.7
70	21	32.1	33.4	40.6	48.2
75	90	33.0	33.3	39.2	45.2
75	12	33.0	34.1	39.2	47.1
80	95	34.2	34.5	38.6	40.2
80	12	33.4	34.4	39.1	44.6
85	16	33.8	34.9	38.7	41.2
90	15	33.3	34.6	37.6	38.2

Table 16 and figure 11 show the epidermal and subcutaneous temperatures under the particular environmental conditions before the application of heat. If the relative humidity were high, i.e. between 75% and 95%, there was a slight temperature gradient across the skin, and the skin temperature showed a steady increase with increased environmental temperature between 60° F and 80° F. If the relative humidity were low, i.e. between

12 and 21%, there was no temperature gradient across the skin at 60° F and a marked gradient at all higher levels. The skin temperature showed an increase up to 85° F and then a slight drop at 90° F.

Table 16 and figure 12 show the epidermal and subcutaneous temperatures at the sweating threshold with various levels of environmental temperatures and humidities. The threshold of sweating shows no marked change between an environmental temperature of 60° F and 70° F. Above the environmental temperature of 70° F there is a marked and progressive fall of the sweating threshold (epidermal temperature) with a much less marked fall of the subcutaneous threshold temperature. At 80° F and high humidity and at 90° F and low humidity general sweating obscures the local response.

The difference of relative humidity between 12% to 21% on the low side, and 75% to 95% on the high side has a very pronounced effect on the sweating threshold, the threshold at low humidities being higher at all environmental temperatures. The corresponding subcutaneous temperatures show a less marked but otherwise similar influence of environmental conditions.

Measurement of skin resistance with a neuro-dermometer (Style No. 2, A. R. Spartana, Baltimore) showed that at all environmental temperatures tested, increased humidity lowered the electrical resistance of the skin. Environmental temperature had no definite effect on the skin resistance between 60° F and 75° F, but above 75° F there was a marked fall of skin resistance.

A consideration of the foregoing observations suggested the question of whether the observed differences of sweating threshold were in reality only differences of skin capacity for heat and of thermal conductivity and whether these differences could be explained by a fixed

temperature threshold at a fixed depth in the tissues. With this idea in mind graph 13 was plotted. This graph shows the temperature on the abscissa and the tissue depth on the ordinate. For the various environmental conditions the mean epidermal temperature at the sweating threshold and the mean subcutaneous temperature at sweating threshold were plotted and connected by straight lines. These lines indicate the heat loss in the process of tissue penetration. If there should be an absolute threshold for local sweating response each line should pass through that point. Theoretically this point where the lines cross should give the absolute temperature threshold and the anatomical depth of this threshold. This assumes that the skin is a homogenous medium in respect to heat conduction which is definitely not true. It assumes further that the subcutaneous temperature was always measured at exactly 1 mm depth, which is not true either. However, it was felt that such a procedure might indicate the possible existence of a fixed local intradermal temperature threshold for sweating. Regardless of the criticism of the method, the results of the graph suggest an optimum depth between A and B, which corresponds to a skin depth of about 1.3 mm and a temperature of about 38° C.

Local sweating response can be elicited easily by the local injection of parasympathomimetic drugs. This is naturally not connected with any rise of skin temperature and on the other hand we have no reason to believe that the heat response is mediated by some chemical metabolite. Therefore the study was next directed to ascertain the effect of various drugs on sweating induced by the local application of heat.

If the local sweating response is due to the direct effect of the heat on the sweat glands, then atropine acting as an acetylcholine inhibitor should not influence this response. Experimentally it was

found that 1.2 mg of atropine injected subcutaneously (in the opposite arm) raised the threshold from an epidermal temperature of 39.4° C (Fig. 14 A) to 45.2° C (Fig. 14 B). This indicates that there is no absolute threshold for local sweating and suggests that there is a facilitation mechanism of the local heat response with that of the nervous regulatory apparatus.

With this idea in mind it was attempted to change the epidermal temperature threshold for sweating by other means. 0.1 cc of acetylcholine 1:100,000 and 1:500,000 was injected intradermally at the site to be tested and it was found that this consistently lowered the threshold of local sweating from 44.6° C to 39.8° C and 42.2° C, respectively.

When acetylcholine 0.1 cc of a solution 1:1 million was injected a marked sweating response was obtained (Fig. 14 C). This response lasted for 30 to 40 minutes. After one hour by which time sweating had entirely subsided, a subthreshold amount of local heat was applied (40.6° C for two minutes) and a definite sweating response was obtained (Fig. 14 D). When acetylcholine 1:1/2 million and 1:1 million was injected in the same way, it was found that the amount of sweating increased with high environmental temperatures and it decreased by the systemic administration of atropine.

The local injection of procaine, 0.1 cc of the 1% solution and of 0.1 cc of hexamethonium (Bistrinum, Squibb, 25 mg/cc) at the site to be tested consistently raised the thermal threshold for local sweating. None of these agents abolished the sweating response.

The literature on the local sweating response to local application of various agents is rather contradictory. It is felt on the basis of these findings that this is due to the fact that the influence of

environmental conditions was usually overlooked, and that drugs were used for stimulation of the sweating response. The intradermal injection of drugs always presents difficulties of quantitation, of concentration and of depth of injection. Therefore it is more difficult to work at a threshold level with drugs than it is when heat is applied with an instrument like that employed in these studies. The apparent contradictions in the literature also may be explained in part by mutual facilitatory action of the local response and the nervous control of sweating. With a strong local stimulus no facilitation is necessary to produce sweating; but with a minimal or even subliminal stimulus facilitation by environmental and pharmacological factors will determine the response.

f) The relationship between the various reactions

So far only individual reactions to local heat application have been determined. At this point it will be attempted to discuss the relationship or non-relationship between the various reactions.

The sensation of heat will be left out of this discussion, as no concept of this sensation clearly defined in physical units could be obtained.

The temperature threshold of local sweating is markedly influenced by environmental temperature and relative humidity. The same does not apply to the sensation of pain or any of the injury reactions studied. In the sweating reaction the time of heat application is important. The same applies to some extent to the severe injury reactions, while in skin flare and in the pain sensation time of heat application does not effect the temperature threshold. Hence at high environmental temperature with high relative humidity and prolonged heat application sweating can be produced without injury, without pain, and without skin flare. On the other hand with low environmental

temperature, with low relative humidity and short periods of heat application no sweating can be obtained even by going beyond the blister threshold. The conclusion of these observations is that sweating and the control of the local sweating response are not related to any of the other reactions examined.

In regard to the relation of skin injury to pain, it is clear from the previous observations that macules, papules, and blisters cannot be produced without pain. Not so clear is the relationship between skin flare and pain. The previous discussion indicated that these two phenomena may be related physiologically, but our knowledge of their actual causation and nature is still very fragmentary. Objective scientific investigation of the relationship between pain and injury has been hampered by the philosophical concept of the usefulness of pain. If pain is useful it should not occur without injury, and to make it still more useful no injury should occur without pain. Wolff (151,152) discusses the history of this problem. In their own work Wolff and Hardy (61, 151) concluded that injury cannot be produced without pain. As the observations of pain presented here disagree with those of the Wolff and Hardy group, it was decided to reexamine this problem of the relationship between pain and skin flare.

For this study conduction heat and radiation heat were used at various levels of heat energy input. The procedure was similar to that of the previously described pain experiments except that heat was applied until a predetermined temperature level was reached. Then the probe was removed from the skin, skin flare was determined by visual inspection, and pain by questioning the subject. For each heat energy level a number of experimental runs were made, so that the final surface temperatures reached at the end of each determination covered a range of 42° C to 60° C

at intervals of 1° C. The determinations did not always include this entire range because frequently a definite threshold for pain and for skin flare could be established by a smaller number of tests.

Table 17

The relationship between the threshold of pain and skin flare
10 subjects.

Energy meter readings	Time to reach threshold		Pain Surface temperature at threshold		Subcutaneous temperature at threshold	
	seconds	s.e.	°C	s.e.	°C	s.e.
	20	56	3.0	46	0.5	39.9
25	17.5	0.8	49.8	0.5	39.8	0.5
30	10.2	0.3	51.4	0.6	40.1	0.4
35	8.2	0.2	53.6	0.8	40.5	0.7
40	6.8	0.1	54.2	0.7	41.2	1.0
50	1.8	0.1	58.1	1.2		
			Flare			
20	39.0	1.9	44.3	0.5	38.6	0.5
25	12.8	0.3	45.9	0.5	38.0	0.4
30	8.6	0.3	48.2	0.7	38.2	0.5
35	7.5	0.3	51.8	0.6	39.6	0.5
40	7.2	0.1	58.4	0.8	42.8	0.6
50	4.5	0.1	63.5	1.3		

Table 18

The relation between pain and skin flare. Radiation heat.
10 subjects.

Energy meter readings	Time to reach threshold		Pain Surface temperature at threshold		Subcutaneous temperature at threshold	
	seconds	s.e.	°C	s.e.	°C	s.e.
	5	No pain occurred after 60 seconds exposure				
6	40.1	3.2	50.8	1.7	44.5	0.9
7	9.9	0.6	52.2	0.9	44.0	0.7
8	7.0	0.5	51.6	0.9	44.5	0.7
			Flare			
5	30.2	2.2	46.5	0.9	43.6	0.8
6	14.8	1.3	46.0	0.9	43.7	0.7
7	10.0	0.6	52.0	0.8	43.8	0.7
8	8.7	0.9	52.3	1.0	46.5	0.7

The results are given in tables 17 and 18, and in figures 15 and 16. They show that the times required to reach the threshold for pain and for skin flare are quite close; however, at low intensities of heat energy input the time to reach the threshold for flare is shorter than that for pain, and at high intensities the time to reach the threshold for pain is shorter than that for flare. Inspection of figures 15 and 16 shows that the differences at both ends of the two lines are statistically significant. Furthermore, after the determination of the pattern of reactivity of a subject, it is possible to produce at will in each subject pain without skin flare or skin flare without pain.

Using a high temperature level the temperature changes in the skin are so rapid that it was not possible to determine subcutaneous temperatures with our recording system.

The relative thresholds obtained with conduction and radiation heat correspond very well and show the same pattern. However the absolute values for the epidermal and subcutaneous temperature thresholds show marked differences, those for radiation being higher. It is believed that this is due to the absorption of radiant heat by the thermocouple as discussed earlier.

Another difficulty in the use of radiation heat is the fact that any change of heat intensity causes a change in the emitted wavelength and, therefore, the extent of skin penetration. It is felt in view of these difficulties that all data obtained by the use of radiation heat have only comparative value, while those obtained with conduction heat can be considered as true values.

The findings reported here naturally raise the question whether there is a common physiological basis for flare and for pain. The time-energy curves (figures 15 and 16) do not exclude the

possibility of some common (histamine-like) metabolite being responsible for both. Even if the essential stimulus for both phenomena is the same, the mechanism for their production can still be distinct and the thresholds different. Flare very likely occurs via an axon reflex with the release of an unidentified vasodilator substance at the efferent periphery, whereas the pain impulse travels via the peripheral nerve and the spinal cord to the brain.

The question of whether the terminal ramification of the pain nerves in the skin are the same as the nervous pathway for the axon reflex generally considered to be responsible for flare is unanswered.

The differences between these two reactions demonstrated in these experiments could be explained by the assumption of two different metabolites. These could either effect the same nerve endings at a different threshold, or each might stimulate a different type of nerve. If there are only one metabolite for both reactions, but two different nerve fibers, this would also explain the experimental findings.

Another possibility is that pain may be due to direct stimulation of the nerve endings and that skin flare may be caused via the release of some chemical mediator. In favor of this hypothesis is the quickness of the pain response and the delay of the appearance of skin flare.

The evidence presented does not give any basis to accept or reject any of these theories.

D. Discussion

The findings are discussed at the end of each section. Before coming to a summary of the results it has to be pointed out that throughout these experiments stimulation was produced only over a very

small skin area. Moreover the temperature registration with the especially designed instrument and with thermocouples differs markedly from the radiometer used by Hardy and his group. The radiometer measures heat emission from the skin while in the experiments reported here actual skin temperatures are measured. Therefore the results obtained with one method do not necessarily confirm or contradict those obtained with the other method. The interpretations of experimental data should fit all the evidence available. This aspect of the problem is discussed in the various sections. The conclusions are based on these discussions. Our knowledge in this field is far from complete. No doubt some of these interpretations will have to be modified with the advance of knowledge in this field.

E. Summary and Conclusions

1. An instrument was designed and constructed which allows the application of heat to small skin areas with instantaneous measurement and control of the temperature of the applicator and the energy input necessary to obtain this temperature.

2. In the investigation of heat induced sensations it was found:

- a) The surface temperature at the time the pain threshold is reached is directly related to the heat energy.
- b) The temperature gradient across the skin at the time the pain threshold is reached is directly related to the heat energy.
- c) An analysis of these findings indicates that heat pain is determined by a definite temperature threshold at a point slightly below the skin surface.

d) With heat applied to small areas of the skin no constancy in the threshold determination of the sensation of heat could be obtained.

3. The thresholds for the various heat induced skin lesions were examined regarding time and temperature of stimulation.

Skin flare was found to be determined by the temperature of heat application while the duration of application is relatively unimportant. Skin flare at threshold appears and disappears in 1/2 to 10 minutes.

For macules the duration of heat application is a major factor. The maximum reaction is observed four hours after the heat application.

The duration of heat application is of importance in the production of blisters; and the interval between the heat application and the appearance of the lesion is longer for blisters than for any other injury reaction.

4. The threshold of skin flare was found to be a constant characteristic for each individual. Environmental conditions and changes in blood flow influence the heat energy necessary to obtain the threshold temperature, but not the threshold in terms of temperature. With the advance of age the threshold of skin flare is progressively raised.

5. The following observations were made on the effect of cutaneous site on heat induced injuries and healing:

- a) There are marked differences of injury reaction and healing in various sites of the human body.

- b) A gradient of decreased healing tendency exists down the leg and is diminished by bed rest.
- c) Healing time is reduced by bed rest.
- d) Increased environmental temperatures increases the severity of the injury reaction and promotes healing while cold environment decreases the severity of reaction and delays healing.
- e) The effects of changes of blood supply and blood flow on healing are minor and perhaps due to the change of temperature.

6. The local sweating response can be readily induced by local heat application. This response is greatly influenced by the time of heat application, by the environmental temperature, and by the relative humidity. Parasympathetic, nervous, and ganglionic blocking agents inhibit this response, while parasympathomimetic agents facilitate the sweating response.

These findings were found to support the concept of a fixed temperature threshold for local sweating response at a fixed skin depth. However, this is not an absolute threshold but it is dependent on facilitation and inhibition by the neuro-humoral mechanism, as similarly this neuro-humoral mechanism of sweating is influenced by the skin temperature.

7. The relationship of skin flare and pain were investigated. The temperature thresholds for these two phenomena were found to be very close, but at low levels of energy input the threshold for pain is higher, and at high levels of energy input the threshold for flare is higher. Possible physiological implications of these findings are discussed.

Figure 1

Wiring diagram of model A, or the A C model of the apparatus.

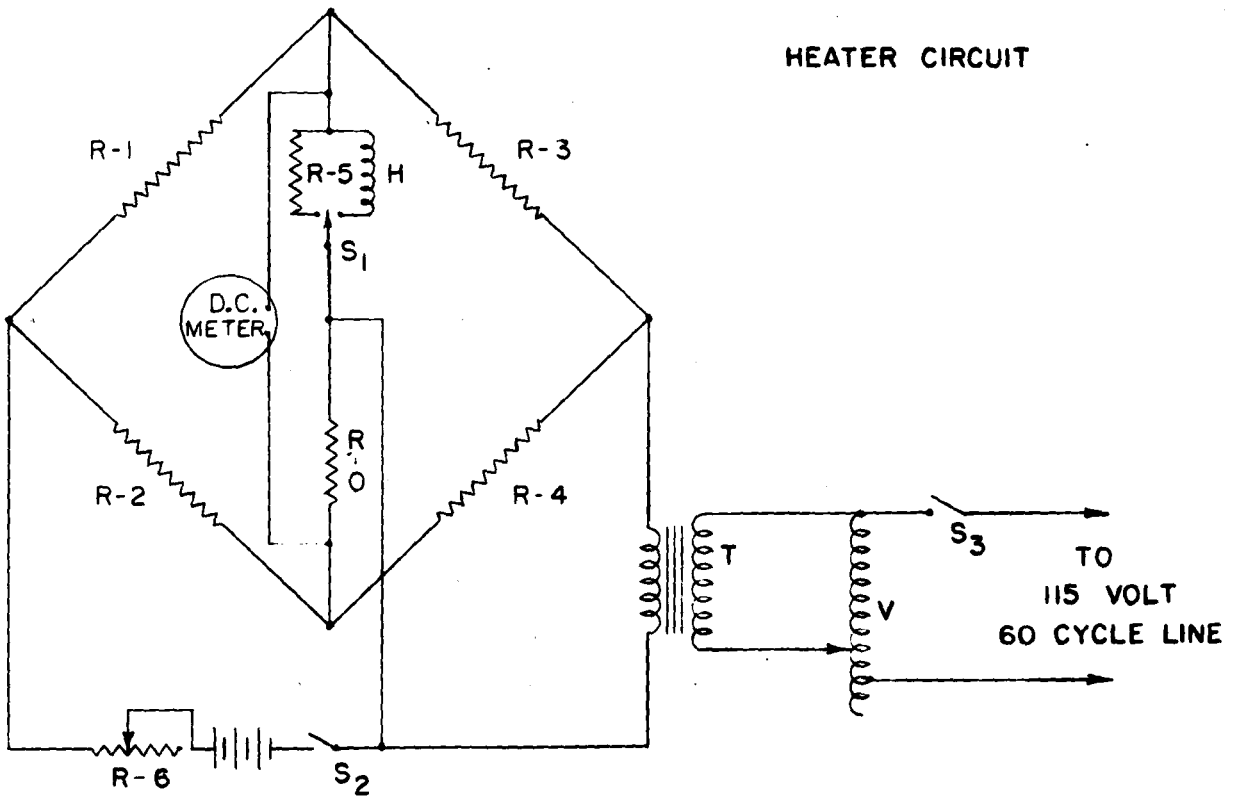


Figure 2

Wiring diagram of model B, or the battery operated apparatus.

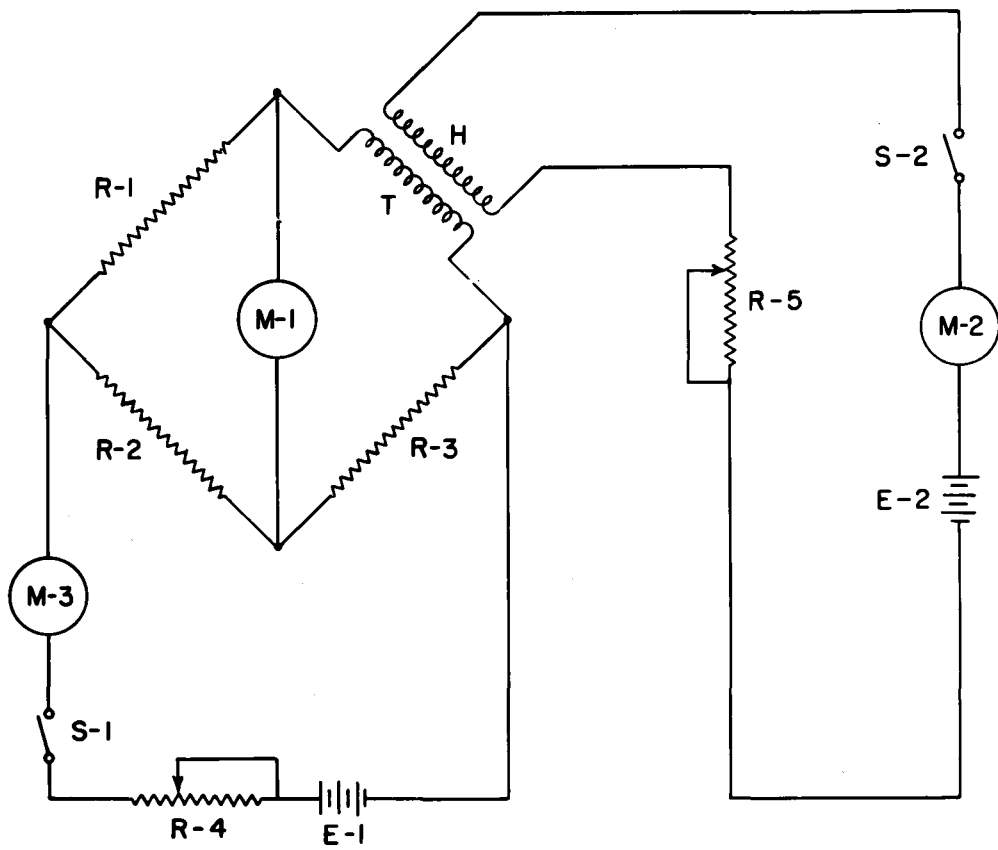


Figure 3

The applicator of the apparatus with weight attached from below.

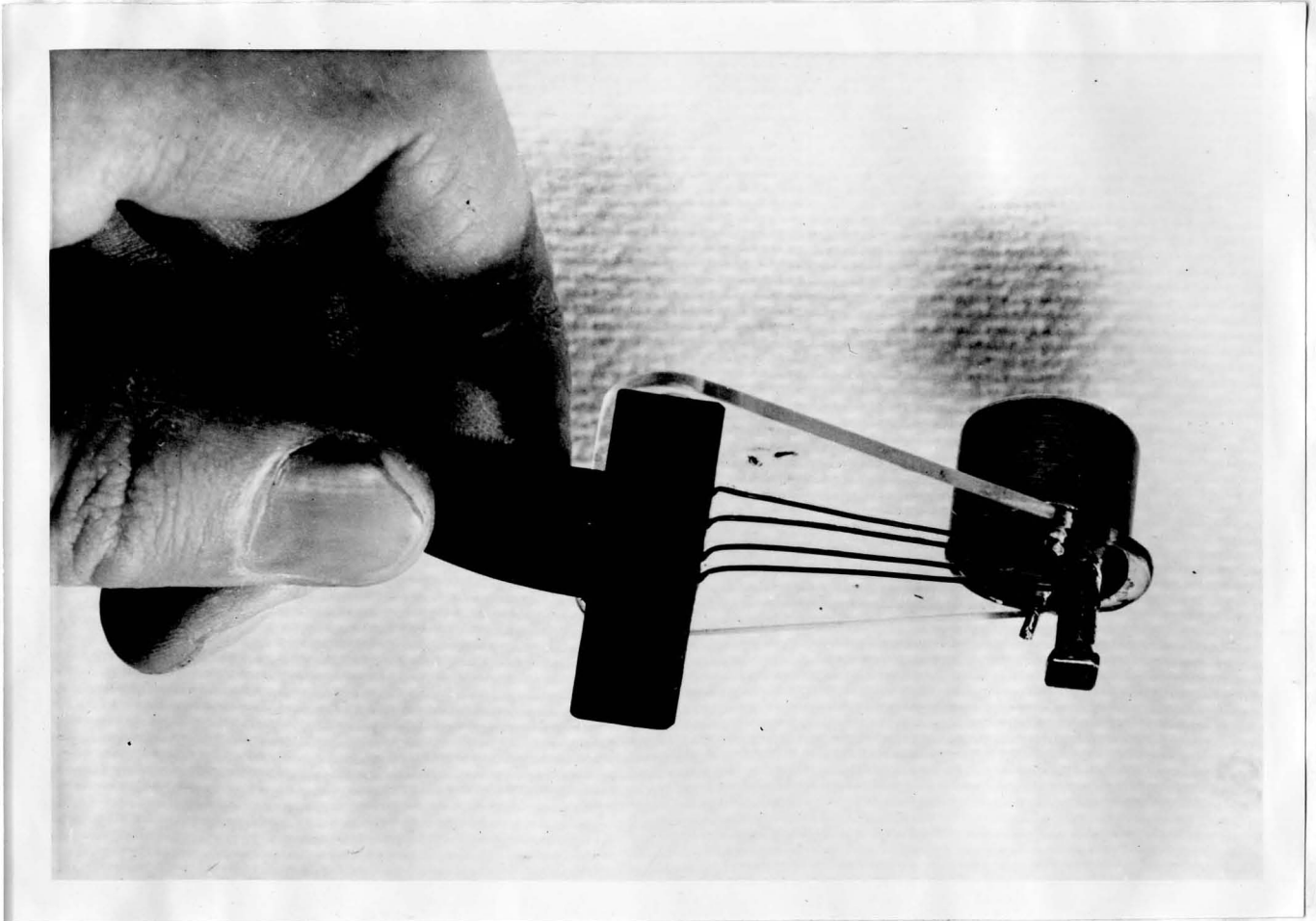


Figure 4

Range of epidermal and subcutaneous temperatures with various energy levels of conduction heat.

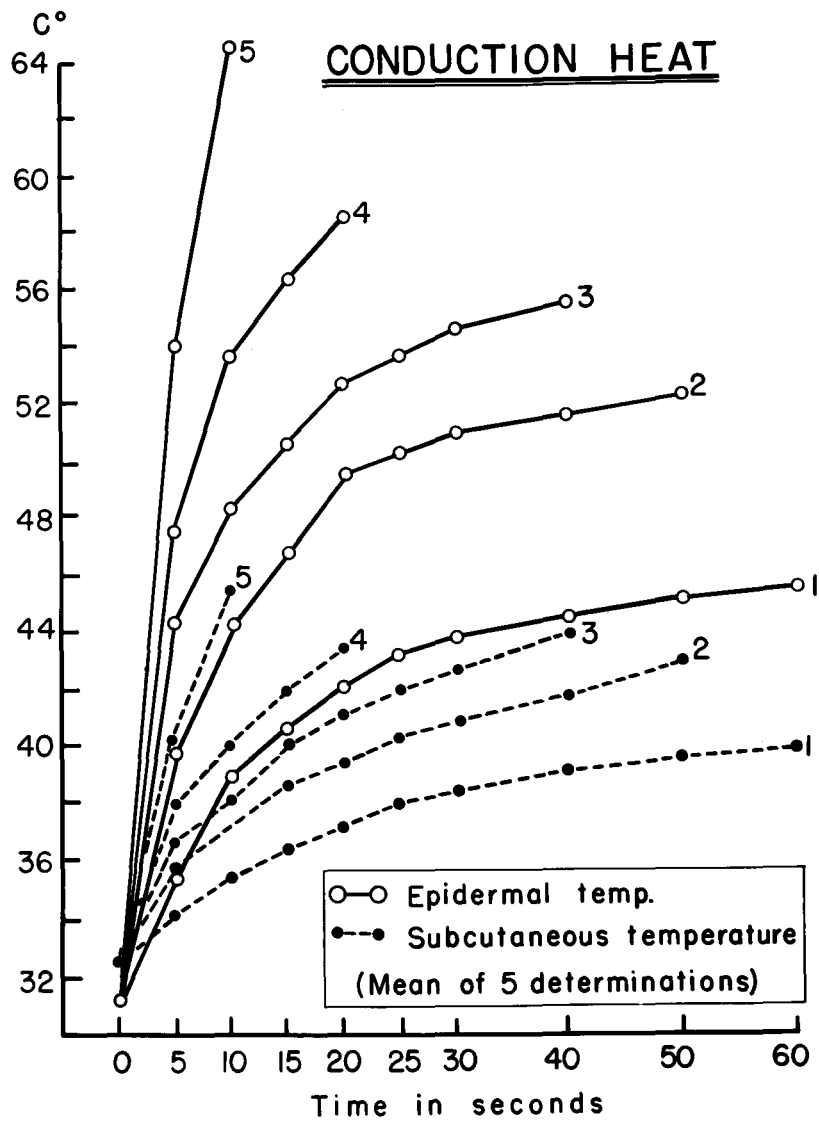


Figure 5

Range of epidermal and subcutaneous temperatures with various energy inputs of radiation heat.

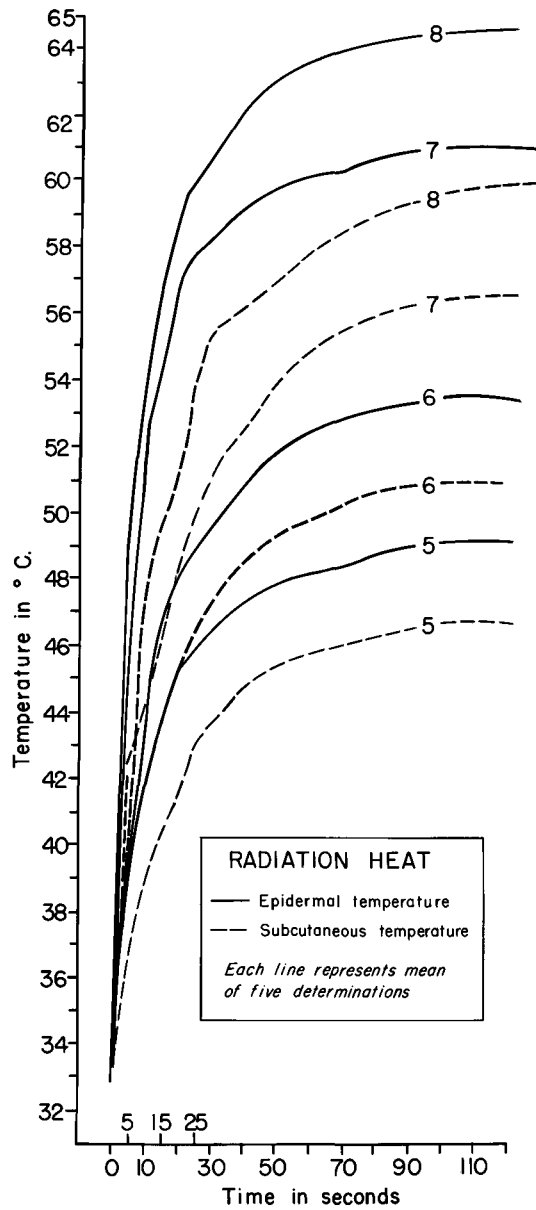


Figure 6

Subcutaneous temperatures occurring at various levels of constant epidermal temperatures.

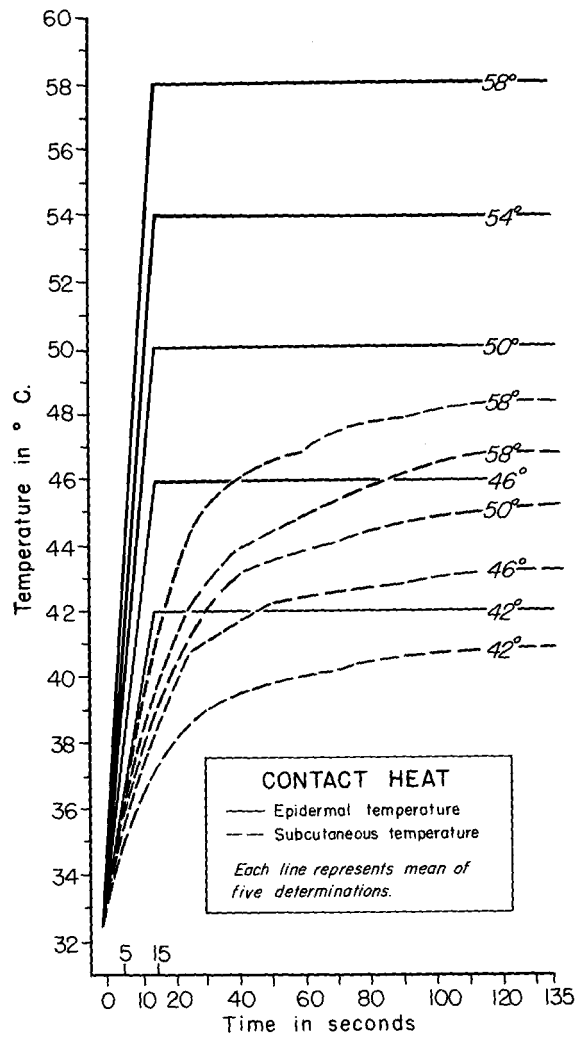


Figure 7

Epidermal and subcutaneous temperatures for two different ranges, indicating that pain (P) occurs at the same subcutaneous temperature independent of the epidermal temperature. (Each point represents the mean of five determinations.)

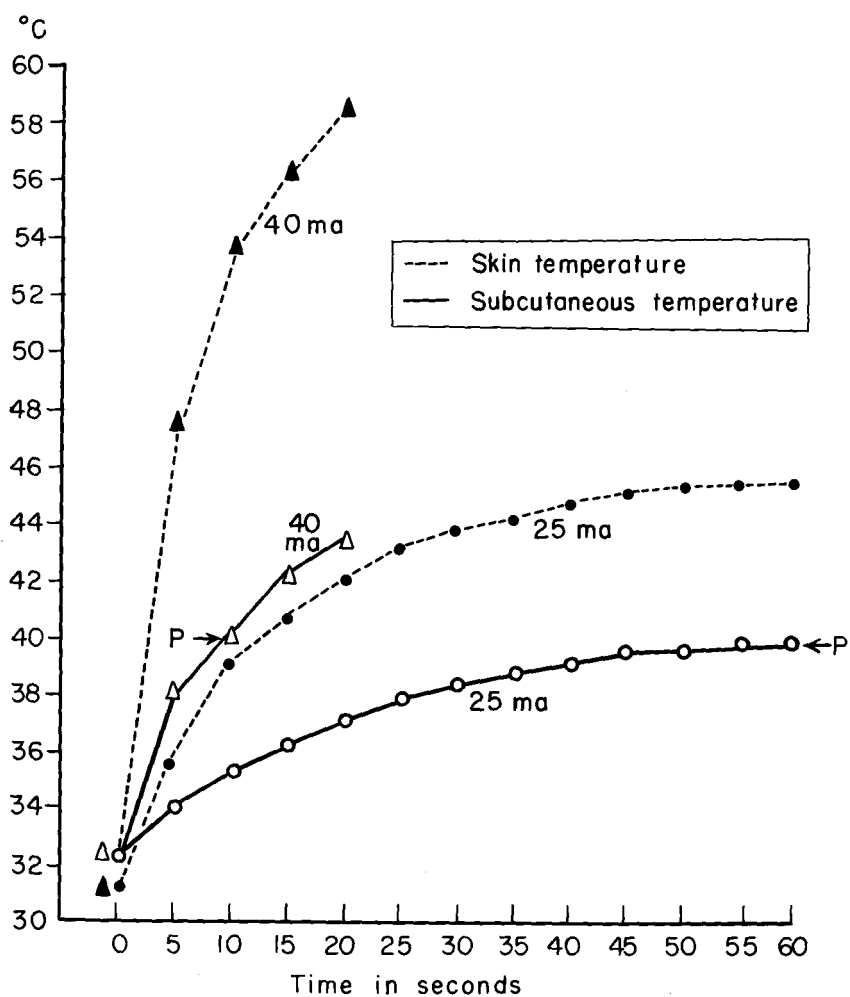


Figure 8

The effect of heat energy on the time to reach the pain threshold and the surface temperature at the pain threshold. For each energy level both points plotted indicate the same pain threshold indicating that the time necessary to reach the threshold decreases with the increase of heat energy, while the surface temperature at threshold increases. (Each point represents the mean of 10 determinations.)

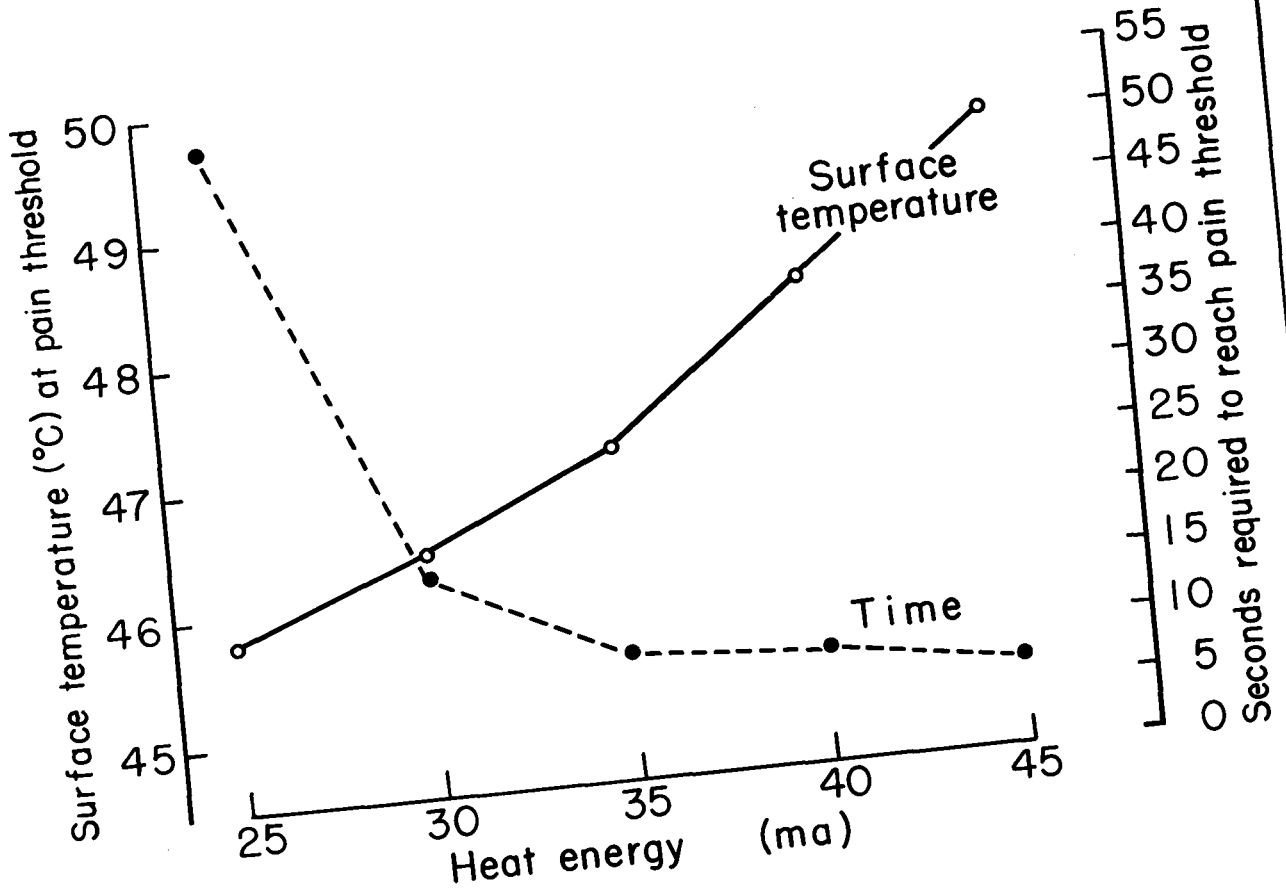


Figure 9

If the surface temperature of the pain threshold is plotted against the time, the result is a typical strength - duration curve. Each point represents the mean of 10 determinations.

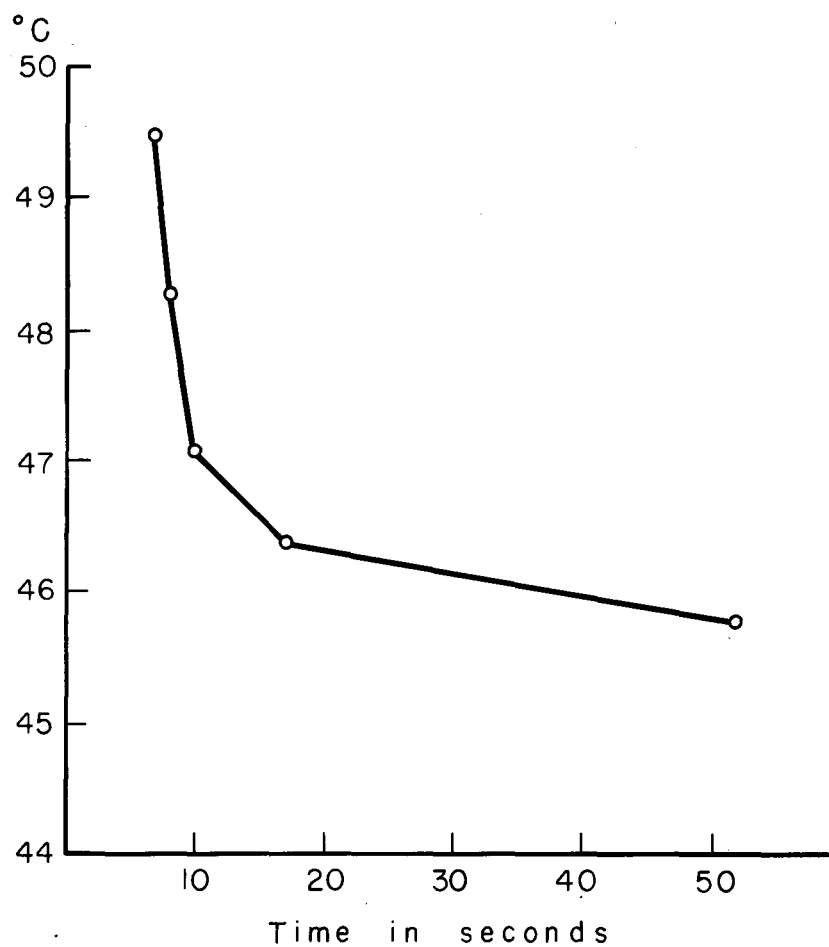


Figure 10

The healing of leg lesions 10 days after injury production.

conditions. Each point represents the mean of 7 or more determinations.

- A. Epidermal temperature at low humidity.
- B. Epidermal temperature at high humidity.
- C. Subcutaneous temperature at high humidity.
- D. Subcutaneous temperature at low humidity.

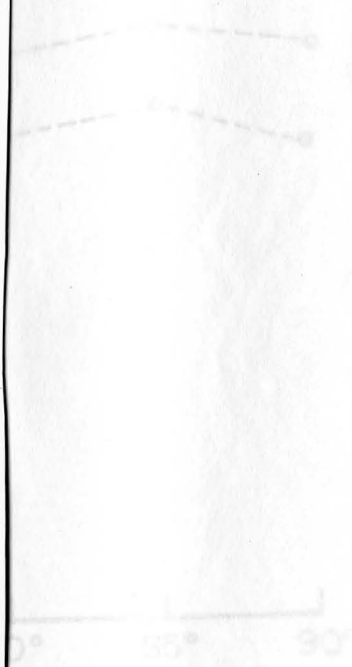
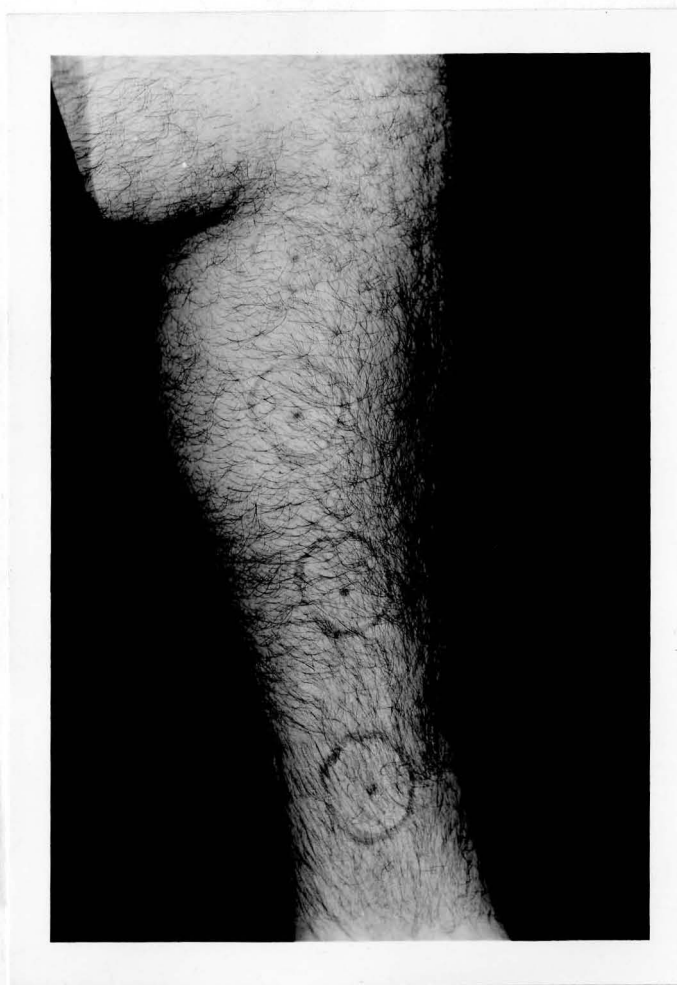
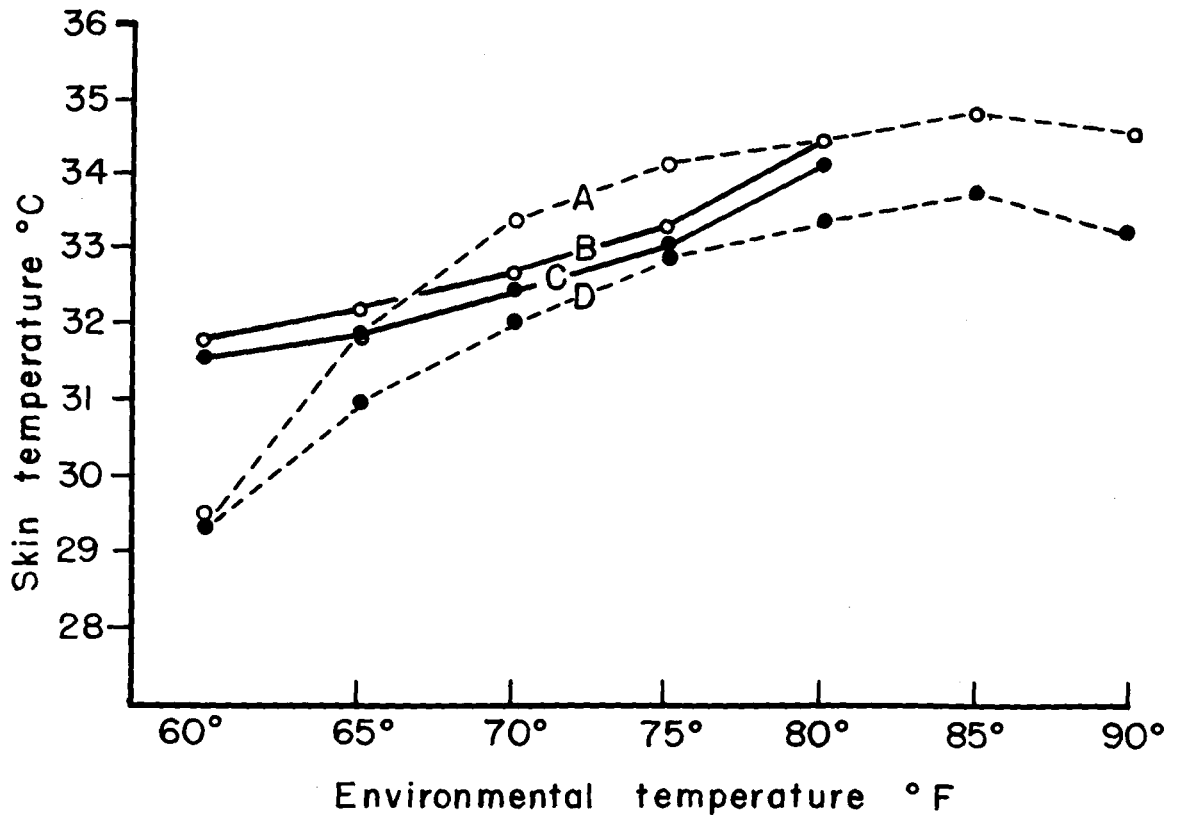


Figure 11

Epidermal and subcutaneous temperatures under various environmental conditions. Each point represents the mean of 7 or more determinations.

- A. Epidermal temperature at low humidity.
- B. Epidermal temperature at high humidity.
- C. Subcutaneous temperature at high humidity.
- D. Subcutaneous temperature at low humidity.



Epidermal temperature and subcutaneous temperature at sweating threshold under various environmental conditions. Each point represents the mean of 7 or more determinations.

- A. Epidermal temperature at low humidity.
- B. Subcutaneous temperature at low humidity.
- C. Epidermal temperature at high humidity.
- D. Subcutaneous temperature at high humidity.

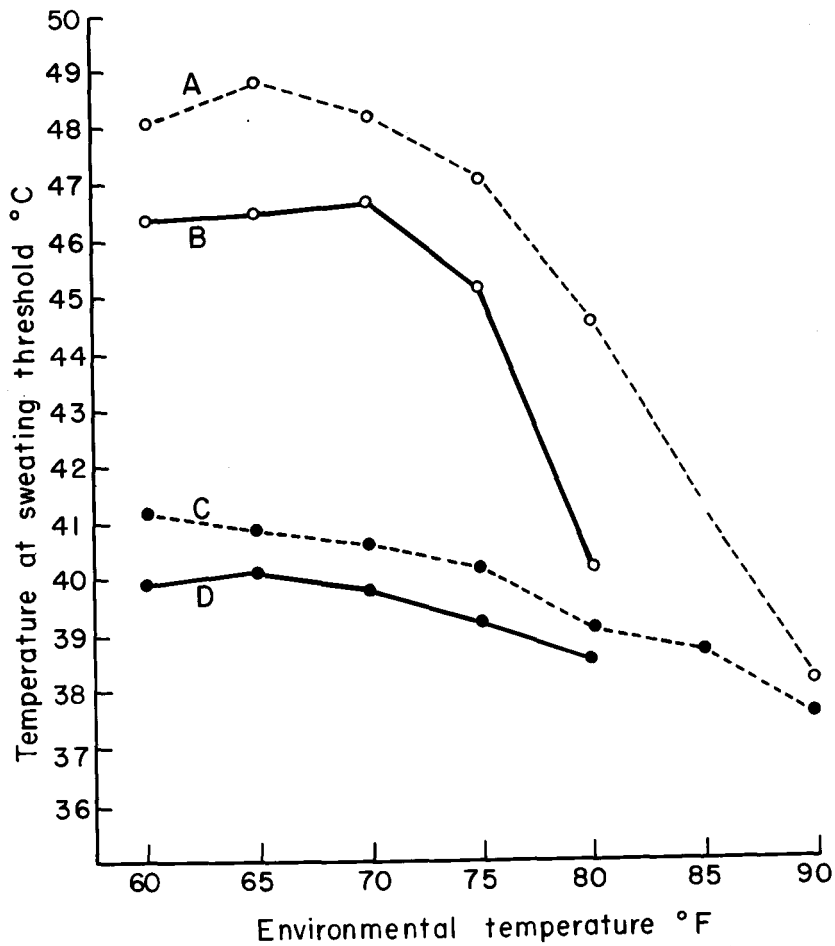


Figure 13

The heat loss in the process of tissue penetration at sweating threshold. The lines come closest together between A and B, suggesting a possible fixed temperature sweating threshold at fixed depth in the tissues.

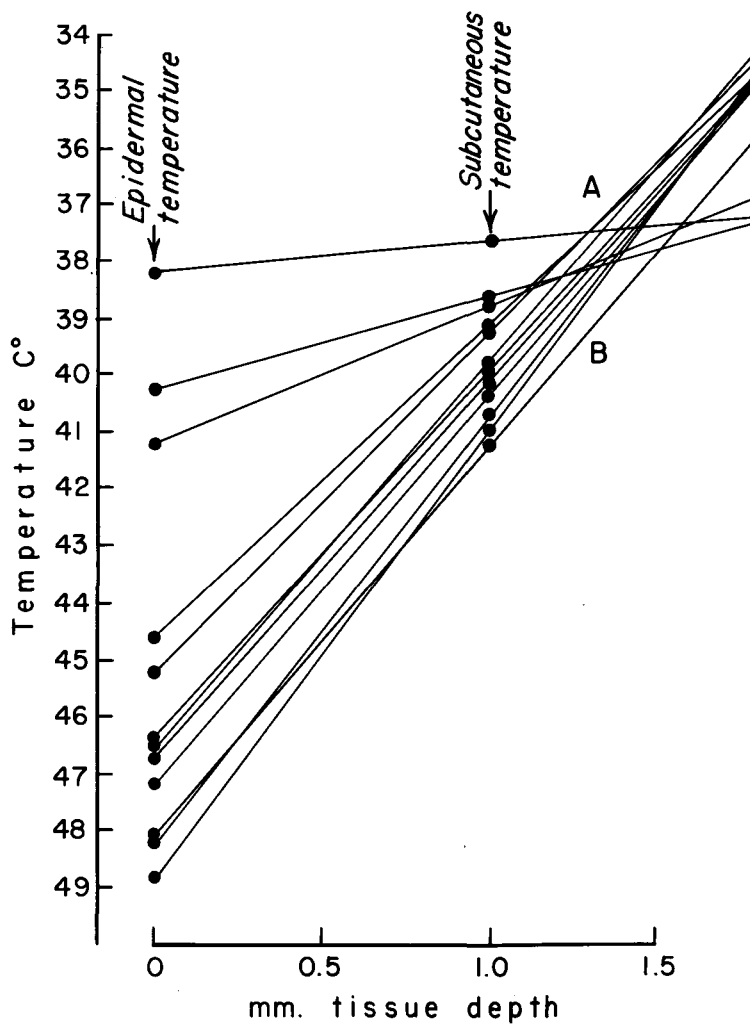


Figure 14

Sweating Response:

- A. Threshold response, 3 minutes at 39.4° C.
- B. After 1.2 mg of atropine the threshold was 45.2° C for 3 minutes.
- C. Response to acetylcholine 1:1 million.
- D. One hour later when the response had subsided, subthreshold heat stimulation of 40.6° C for two minutes produced a definite response.

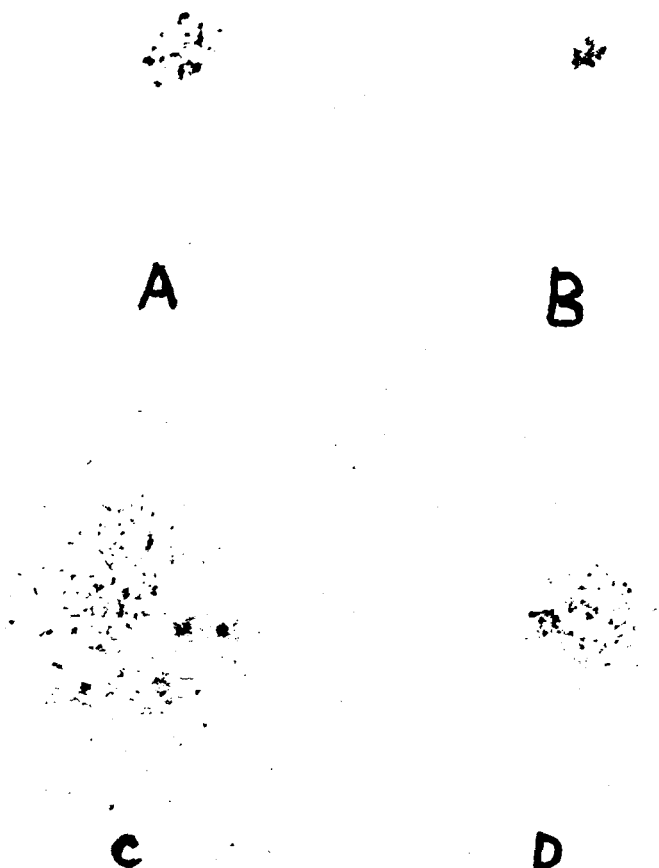


Figure 15

The relationship of the threshold of pain and the threshold of skin flare with conduction heat as the stimulus. Each point represents the mean of 10 determinations. Heat energy is given as meter setting.

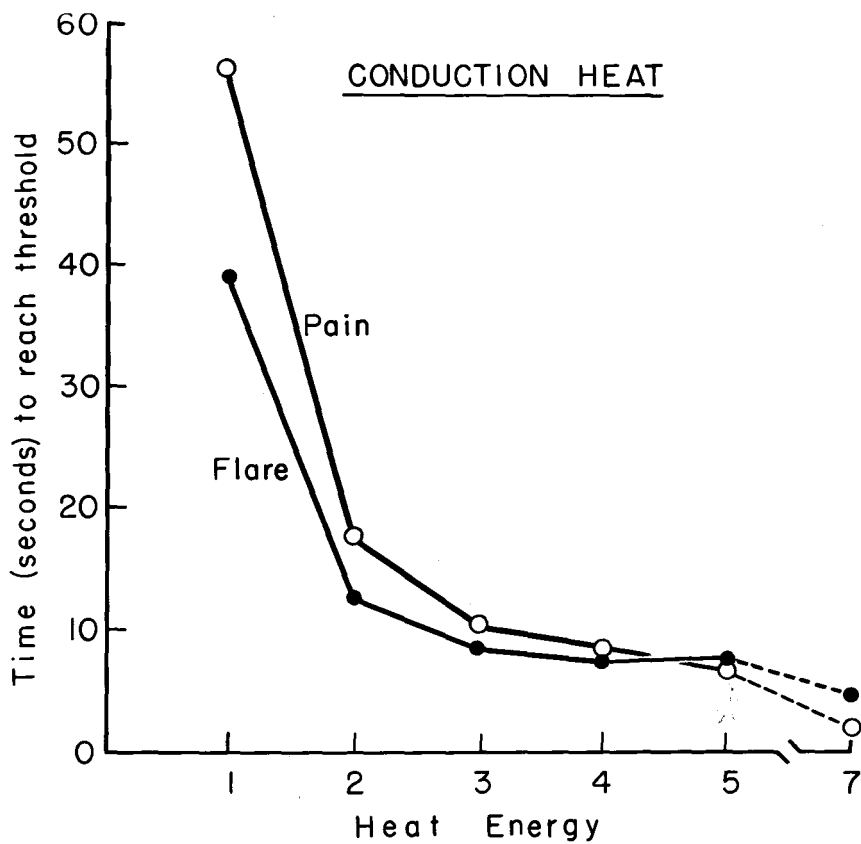


Figure 16

The relationship of the threshold of pain to the threshold of skin flare with radiation heat as the stimulus. (Mean of 10 determinations.)

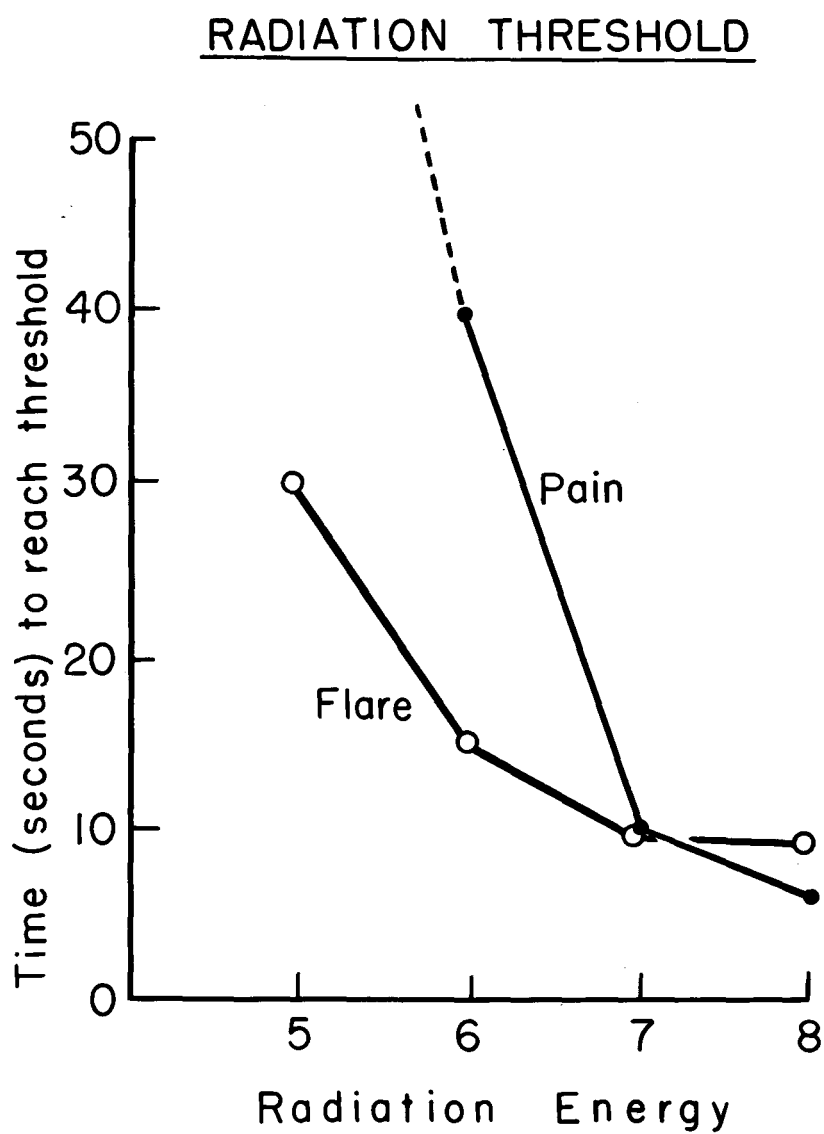


Figure 17

Registration of temperature curve in an experiment under controlled environmental conditions.

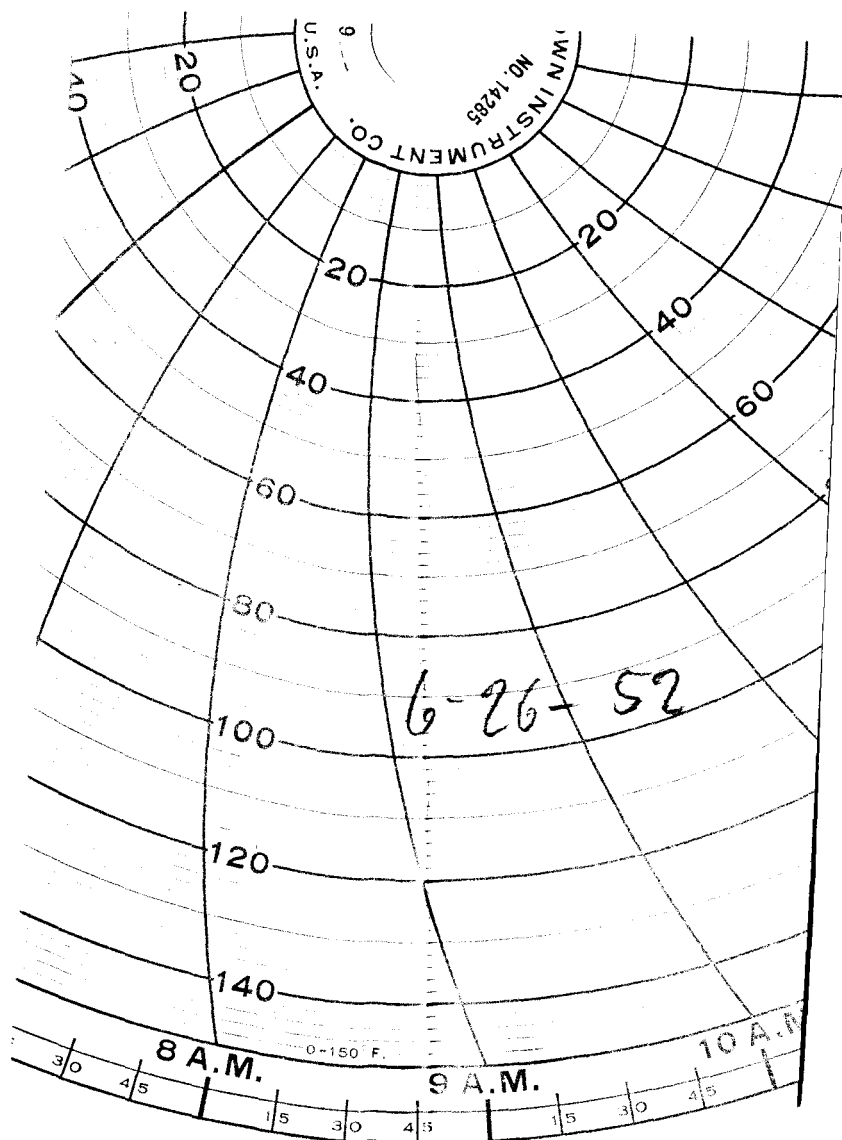
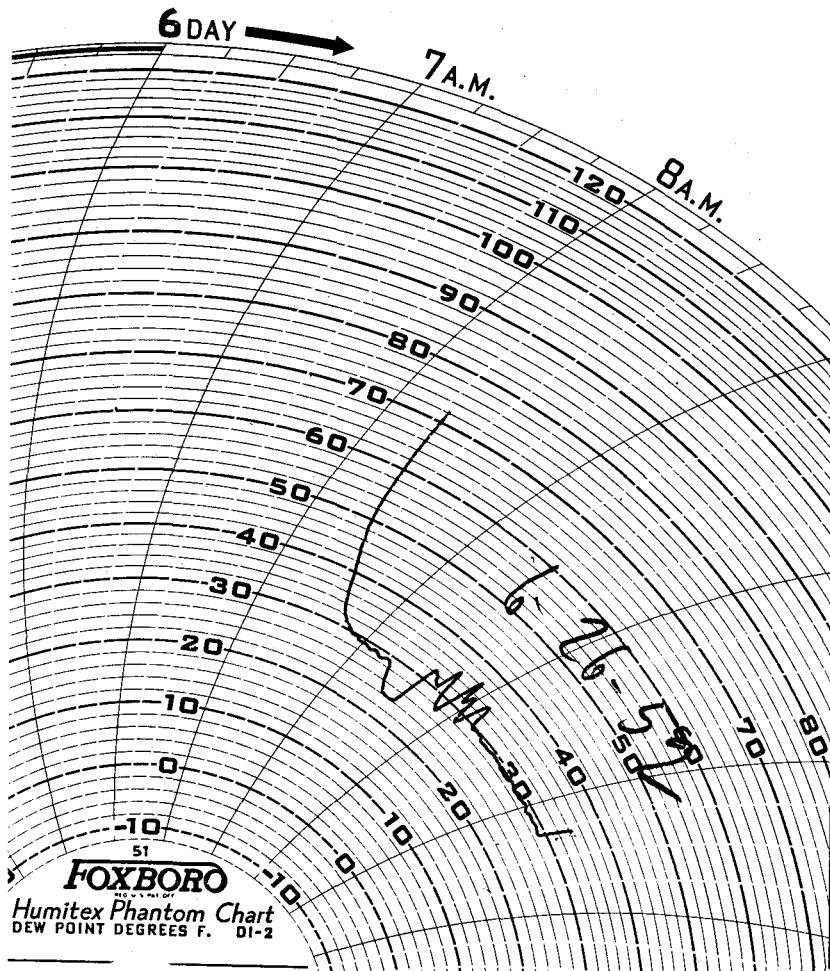


Figure 18

Registration of relative humidity (dew point) in an experiment under controlled environmental conditions.



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THE EFFECT OF LOCAL HEAT APPLICATION ON THE HUMAN SKIN.

Abstract of the Ph.D. thesis by Fred B. Benjamin

This investigation was undertaken to determine the various reactions resulting from the application of heat to small skin areas.

The review of the literature revealed much valuable information. This investigation is an attempt to correlate these findings and fill in the gaps in our knowledge. Therefore a wide range of reactions were studied systematically and with standardized equipment.

The three main groups of reactions studied are:

1. Heat and pain sensations.
2. Injury reactions, i.e. skin flare, macules, papules and blisters.
3. The local sweating response.

Each phenomenon was studied separately in an attempt to determine the relative importance of the duration of heat application, the heat energy, the surface temperature, and the subcutaneous temperature. From the results of these experiments it was attempted to deduce the mechanism of the production of the various reactions and their possible physiological significance. Finally an attempt was made to examine possible interrelationships between the various reactions.

An instrument was especially designed and made to allow the application of contact heat to small skin areas with instantaneous measurement and control of the temperature of the applicator and of the energy input necessary to obtain this temperature. The applicator was calibrated to give as nearly as possible the temperature of the underlying skin.

Comparative values were obtained with a radiation beam concentrated to a small skin area. Subcutaneous temperatures were taken with needle thermocouples connected to a self balancing Brown potentiometer.

The results can be summarized as follows:

1. In the investigation of heat induced sensations it was found:

a) The surface temperature at the time the pain threshold is reached is directly related to the heat energy.

b) The temperature gradient across the skin at the time the pain threshold is reached is directly related to the heat energy.

c) An analysis of these findings indicates that heat pain is determined by a definite temperature threshold at a point slightly below the skin surface.

d) With heat applied to small areas of the skin no constancy in the threshold determination of the sensation of heat could be obtained.

2. The thresholds for the various heat induced skin lesions were examined regarding time and temperature of stimulation.

Skin flare was found to be determined by the temperature of heat application while the duration of application is relatively unimportant. Skin flare at threshold appears and disappears in one-half to ten minutes.

For macules the duration of heat application is a major factor. The maximum reaction was observed four hours after heat application.

The duration of heat application is of importance in the production of blisters; and the interval between the heat application and the appearance of the lesion is longer for blisters than for any other injury reaction.

3. The threshold of skin flare was found to be a constant characteristic for each individual. Environmental conditions and changes in blood flow influence the heat energy necessary to obtain the threshold

threshold temperature, but not the threshold in terms of temperature. With the advance of age the threshold of skin flare is progressively raised.

4. The following observations were made on the effect of cutaneous site on heat induced injuries and healing:

a) There are marked differences of injury reaction and healing in various sites of the human body.

b) A gradient of decreased healing tendency exists down the leg and this is diminished by bed rest.

c) Healing time is reduced by bed rest.

d) Increased environmental temperature increases the severity of the injury reaction and promotes healing while cold environment decreases the severity of reaction and delays healing.

e) The effects of changes of blood supply and blood flow on healing are minor and perhaps due to the change of temperature.

5. The local sweating response can be readily induced by local heat application. This response is greatly influenced by the time of heat application, by the environmental temperature, and by the relative humidity. Parasympathetic, nervous, and ganglionic blocking agents inhibit this response, while parasympathomimetic agents facilitate the sweating response.

These findings were found to support the concept of a fixed temperature threshold for local sweating response at a fixed skin depth. However, this is not an absolute threshold but it is dependent on facilitation and inhibition by the neuro-humoral mechanism, as similarly the neuro-humoral mechanism of sweating is influenced by the skin temperature.

6. The relationship of skin flare and pain were investigated. The temperature thresholds for these two phenomena were found to be very close, but at low levels of energy input the threshold for pain is higher, and at high levels of energy input the threshold for flare is higher. Possible physiological implications of these findings are discussed.