OBSERVATIONS ON SOME NORMAL AND INJURIOUS EFFECTS OF COLD UPON THE SKIN AND UNDERLYING TISSUES

I. REACTIONS TO COLD, AND INJURY OF NORMAL SKIN*

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The need to understand the reactions of the human skin and underlying tissues to cold increases with time. Men ascend to greater heights on mountain and in air; they go down to work deeper beneath the surface of the sea; and in these ascents and descents they become more exposed to the influence of cold. They work in the artificial coldness of storage chambers. And in wartime many are exposed to the cold of wet trenches or to the icy waters of the sea for long periods. Women, for their part, reduce to vanishing-point the clothing which long experience has taught us it is wise to wear on the limbs in wintry weather. It is my purpose in these lectures briefly to review work relevant to the injurious effects of cold, work that has occupied the attention of my co-workers and myself from time to time for a number of years.

Cooling and its Effects on Blood Flow to the Skin

If a person who is comfortably warm—that is to say, with skin temperature everywhere within a few degrees of blood heat—enters and sits at rest in a cold room the temperature of the skin begins to fall. In the absence of an obvious source of radiant heat, a room temperature of 16° C. (61° F.) will cause progressive cooling in most people; in many it will take place at 18° C. (64° F.); in some it will occur at 20° C. (68° F.). This progressive cooling is shown chiefly by certain parts of the body, where it will continue until the temperature approaches that of the surrounding air. Parts of the body so affected are those presenting a surface that is large in relation to their mass. The extremities of the limbs, and especially the digits, cool fastest and most. Of the face, the ears and nose cool most rapidly, for they, too, have relatively large surfaces; but they do not cool as fast or as far as the digits (Lewis, 1931). The rate and degree of cooling are usually displayed in the order: fingers (and toes), ears, and nose. These are the only parts of the body in which cooling is usually profound in the circumstances described, and fingers and toes are the only parts in which cooling often occurs down nearly to room temperature. Such cooling takes half an hour or more. The presence of clothing naturally influences the result, especially if the air of the room is in motion, for clothing holds a layer of warmer air on the skin's surface. Out of doors in a cold wind, if the subject is walking, the feet will be kept warm by the friction and by increased blood flow to the working muscles of the limb. The fingers and ears in such conditions will cool most, and the fingers more than the ears if the former are uncovered. There will be variations, according to the precise circumstances of exposure and

from subject to subject. Immersion in water brings the skin near to the temperature of its surroundings in a very few minutes, and much faster than exposure to cold air, though again more rapidly and more completely in parts that, like the digits, have large surfaces.

Effect on Blood Flow.—When the body surface is exposed to cold the vessels of the skin normally contract, blood flow is reduced, and heat loss from the skin is diminished. This vasoconstriction is a complex response; indeed, it comprises three separate reactions. First, there is a direct and persistent response of the superficial vessels to cold; they contract locally. Secondly, cold when applied to any part of the skin causes an immediate general vasoconstriction by reflex action through the central nervous system. This reflex, however, is only transient. It is succeeded and replaced by the third response. Cold venous blood returning from the cooled skin joins and lowers the temperature of the blood in the general circulation. This blood travels to, and acts upon, a central nervous mechanism, which is very sensitive to cold and responds by calling forth a general vasoconstriction, which is persistent. The second reaction is easily displayed; for if a limb is cooled while the circulation to it is cut off there is an immediate and transient general vasoconstriction; but the third reaction takes place only when the circulation to the cooled limb is restored (Pickering, 1932). In these vasoconstrictions, whether brought about locally or generally, all surface vessels—arteries, arterioles, capillaries, venules, and veins—participate.

All blood passing through the capillaries of the skin must come to the surface and enter the dense networks of the subpapillary venule plexuses, the blood in which gives colour to the skin. These plexuses act as efficient radiators when blood flows rapidly through them. There is, too, in certain parts of the skin an additional apparatus for heat dispersal—namely, the arteriolo-venous anastomoses, which, situated mainly at the very extremities of the limbs or digits, are able to convey a torrent of blood close to the surface. These additional radiators also respond to cold both directly, and indirectly through the nervous system, and so by closing form part of the mechanism of heat conservation (Grant, 1930; Grant and Bland, 1931; Grant and Pearson, 1938). Briefly, the skin is a most important organ in the regulation of body temperature; for, while it can rapidly dissipate heat when the body should be rid of it, it can conserve heat when the body should retain it.

The complex mechanism here briefly described constitutes a general defence of the body against cold; but, in thus acting, those parts which contain the radiators are

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sacrificed. For a closing-down of the limb vessels, while safeguarding against excessive fall of body temperature, simultaneously ensures a fall of limb temperature. Moreover, the cooling of the limb, with its contained vessels, brings as it proceeds a greater closure of these same vessels in its train. Thus, locally, a vicious circle is established, which gradually carries the temperature of the limb closer and closer to that of its surroundings.

A fall of temperature to 10° C. (50° F.) or lower always benumbs the skin after a time, so that fine touch sense, and ultimately all touch and pain sense, is lost; it weakens the muscles of the limbs, and particularly those of the hand, by cooling them and their motor nerves; it no doubt interferes with the local proprioceptor mechanism and with fine control of movement, which depends on this. Thus the limb, and especially its extremity, in virtue of its sacrifice becomes a relatively inefficient member. But the sacrifice does not end here; there is abundant evidence, presently to be reviewed, that cooling beyond certain points injures the skin. The skin possesses its own local mechanism, which to a point meets this danger.

The Skin's Local Defence

If a finger is dipped into and held in a mixture of ice and water its surface temperature rapidly falls until it is not far above freezing-point; the deep parts of the skin cool almost as much, and the whole process occupies but a few minutes. When the finger is thus robbed of its natural heat it becomes the seat of pain, and this continues as long as the finger is maintained in its cold surroundings. But in five to twenty minutes the pain lessens; the finger feels comfortable, it no longer feels even cold, and observation shows that its temperature is rising. It becomes the seat of a local vasodilatation (Lewis, 1930). This vasodilatation is short-lived, but while it lasts it is intense enough to raise the temperature of the still-immersed finger 5° C. (9° F.) or even as much as 8° C. (14° F.); and it is sufficiently intense to bring the temperature of the cooled finger—if this is withdrawn from the water—well above that of the uncooled fingers of the same hand. This response of the cooled finger does not persist; for vasodilatation, with its warmth, is succeeded by a swing back towards a more usual vascular tone, and at once the temperature of the immersed finger begins to fall again and, cooling sufficiently, the whole process is repeated. Thus the temperature of the immersed finger rises and falls periodically; but as a result its mean temperature is very appreciably raised.

This vascular response of the skin happens not only when digits (fingers or toes) are immersed but when skin of the face, notably that of the ears, chin, and nose, is cooled excessively either by immersion in cold water or by exposure in cold air or wind (Lewis, 1930, 1931). It is a response which is far less in evidence in the skin of the rest of the body. It depends upon a local or axon reflex, for it does not occur in fingers the cutaneous nerves of which have degenerated; it is lost six to ten days after such nerves are cut—namely, at the time at which degeneration happens (Lewis, 1930; Lewis and Pickering, 1936). It returns when these nerves regenerate. The persistent coldness of fingers which have lost their nerve supply is in large part due to the absence of this reflex; and persistent coldness is thought to be responsible for much of the pathological change which is apt to occur in such fingers (Lewis, 1930; Lewis and Pickering, 1936).

The defensive reaction of the skin described is vigorous when cooling proceeds near to the freezing-point of water; but careful observation shows that it begins to be recognizable at temperatures as high as 15° C. (59° F.) or occa-

sionally even 18° C. (64° F.). Thus it happens at temperatures which skin of digits often experiences out of doors during winter months in this country; and the reaction has been shown actually to occur in such circumstances. It is very notable in the hands after snow has been much handled. The response undoubtedly constitutes an important defence against cold, though it will be understood that the defence is incomplete. It appears when cold begins to produce effects on the skin which independent evidence suggests may result from injury. The defensive response to excessive cooling which we are discussing is almost certainly an actual reaction to injury, and related in its degree to the extent of injury.

Evidence that Cold Injures Normal Skin

It is important fully to realize that cold affects the normal skin in two distinct ways. It may damage the skin by direct action or by causing it to freeze. These two effects have often been confused; both have often been described under the term "frost-bite." To avoid such confusion I shall limit that term strictly to effects which follow freezing of the skin, and shall defer consideration of this subject until later. Here I propose first to discuss experimental evidence that normal skin can be injured by reduction of its temperature and without the intervention of a mechanical injury to the cells such as inevitably happens when ice crystals form in the skin. The evidence in question is derived from a number of different sources.

Axon Reflex.—It has been stated already that the skin reacts when cooled to low temperatures. It reacts by producing a local vasodilatation through a local or axon reflex. Now, this reflex is known to be called into play in a large number of other skin reactions: these involve injury of the skin, such as cutting, pricking, burning, freezing, etc., all of which are believed to release histamine-like substance or substances from the skin cells; or the reaction occurs when extracts of skin, or histamine itself, is introduced into the skin. The appearance of a similar vasodilatation on cooling the skin may not be conclusive, but it is suggestive evidence of H-substance release, and to this extent supports the idea of injury (Lewis, 1930).

Local Pain and Tenderness.—Experience would seem to show that in general the production of pain in skin involves damage to the skin. Thus, if heat is applied to skin the earliest evidence of injury, as displayed by vascular reactions, appears at about 42° C. (Lewis and Love, 1926) or very close to the lowest temperature at which the sense of warmth is replaced or supplemented by sense of pain; this temperature is approximately 43° C. (109° F.). Similarly, cold objects give a pure sense of coldness, until as the testing temperature is lowered an element of "sting" or pain is introduced. This new element in the sensory response begins to be detectable very close to the point at which an application of cold to the skin brings the axon reflex response just described—namely, about 15° C. (59° F.).

If a finger is immersed in ice-cold water, pain in it shortly becomes severe enough to be disagreeable, and a finger that has been so treated for a period of, say, ten minutes is subsequently tender and may remain so for many hours (Lewis, 1933). Sometimes in the finger that has been cooled severe burning pain is felt after it has been withdrawn from the ice-cold water; that is so if it is allowed to warm up again too quickly. This pain of recovery can be avoided by re-warming the finger very gradually. The tenderness referred to is unrelated to the pain of re-warming; it appears equally in fingers that are re-warmed slowly and painlessly.

Local Redness.—Two small cubes of ice are laid flat upon the forearms for five minutes; the ice is then removed and both forearms are plunged into water at 30° C. (86° F.), the circulation to one arm being stopped by means of a pneumatic armlet distended on the upper arm. The cooled area on the arm to which the circulation is free becomes red, and this sharply outlined redness disappears gradually in the space of about ten minutes. If now the circulation to the second arm

is released the patch of redness presently becomes defined; this redness disappears in about ten minutes after the circulation is released. Thus the reddening of the cooled forearm is not a direct response of the vessels to cold, for it can persist long after the skin has become warm again. It is due, so it is suggested, to the release of vasodilator substance or substances in the skin as a result of cellular damage; this substance is held *in situ* in the one arm, and its effects begin to decline only when, the circulation being restored, the substance begins to be removed (Lewis,* 1930).

Supercooling.—The skin, as will be described later in more detail, can be cooled below its freezing-point without freezing. It occasionally happens that such supercooling is followed by the formation of an acute wheal and flare on the skin (Lewis and Love, 1926). Such a reaction, were it a usual phenomenon, would in itself form conclusive evidence that the normal skin is directly injured by cold; for the reaction typifies the response to injury. But it is not a usual, it is an exceptional, phenomenon, depending on conditions that are still undefined. For that reason no further conclusion can be drawn from this evidence than that in subjects who display this conspicuous reaction cold can directly injure the skin.

Sensitivity to Cold.—A similar limitation applies to evidence derived from those who show extraordinary sensitivity to cold. In these a piece of ice laid on the skin for a minute is followed by conspicuous whealing. These subjects are rare; some of them suffer simultaneously from paroxysmal haemoglobinuria. The sensitivity of these skins to cold can be reproduced in other subjects by infiltrating the skin of the latter with serum from the original patient (Harris, Lewis, and Vaughan, 1929). The cases are remarkable in that whealing may be produced by temperatures as high as 18° C. (64° F.) or even, as in one case recently seen, as high as 25° C. (77° F.). I hesitate to use these two exceptional instances in evidence of the injurious effects of cold upon skins in general, in that they are not sufficiently understood and may be irrelevant; nevertheless, it is necessary here briefly to describe them, for it is also clearly possible that one or both may be no more than exaggerations of normal reactions.

Prolonged Cooling.—In recent observations I have found that if a normal hand or foot is immersed in water at 5° C. (41° F.) for a period of two hours, at the end of this time the reddened member is quite definitely swollen. The skin is less mobile: when thrown into folds these folds are broad; fine crinkling of the skin cannot be produced by manipulating it. The fingers may be swollen enough to prevent complete or easy flexion of the phalanges—either active or passive flexion. The pulps of the fingers are tenser than usual. The backs of the hands may pit perceptibly; sometimes they pit to an extent that makes it clear that not only skin but subcutaneous tissue is involved. This swelling, which may amount to as much as 15% increase of volume, gradually subsides in a few hours. It is not the simple result of imbibition of water by the skin, though some imbibition by the horny layer undoubtedly occurs, for it happens in a hand protected by grease or by the wearing of a loose rubber glove. It can occur recognizably in hands immersed in water for periods of hours at temperatures as high as 10° or 15° C. (50° or 59° F.). This effect is attributed to an injury by cold; presumably the reaction, as is customary in injury, involves the release of H-substance, which in turn acts on the blood vessels. Here it should be stated that histamine (1 c.cm. of 1 in 30,000 base) injected into the skin of the forearm, deep to the skin, is followed by obvious subcutaneous swelling. If several such swellings are made near to each other, distinct pitting of the arm occurs with firm pressure. Thus release of a histamine-like substance would account for swelling both of skin and of subcutaneous tissue.

In the swelling of a hand to cold, as much as 50 c.cm. increase of volume may be found. It is obvious, therefore, that if several of the limbs become cold for a period of hours, as when immersed in sea water or when submitted to other comparable exposure, a very substantial amount of fluid might be lost from the circulation. Perhaps this reaction may account for or con-

tribute to a state of circulatory collapse in wounded or unwounded men exposed to severe cold.

The observations upon human skin here referred to are all such as arise soon after cooling, and are in the nature of acute reactions of the skin; the reactions illustrate the simplest forms of inflammation, characterized by heat, redness, and swelling. There are in addition a number of conditions associated with more prolonged actions of cold and with more prolonged reactions. These will be considered separately in the next lecture.

REFERENCES

- Grant, R. T. (1930). *Heart*, 15, 281.
 — and Bland, E. F. (1931). *Ibid.*, 15, 385.
 — and Pearson, R. S. B. (1938). *Clin. Sci.*, 3, 119.
 Harris, K. E., Lewis, T., and Vaughan, J. M. (1929). *Heart*, 14, 305.
 Lewis, T. (1930). *Ibid.*, 15, 177.
 — (1931). *Ibid.*, 15, 351.
 — (1933). *Clin. Sci.*, 1, 175.
 — and Love, W. S. (1926). *Heart*, 13, 27.
 — and Pickering, G. W. (1936). *Clin. Sci.*, 2, 149.
 Pickering, G. W. (1932). *Heart*, 16, 115.

FAILURE OF IN VITRO TESTS AS A GUIDE TO THE VALUE OF STORED BLOOD

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Many different solutions are still in use for the preservation of blood during storage. This state of affairs seems to be due mainly to the different criteria that are accepted for the comparison of one solution with another. It will be generally admitted, first, that the value of stored blood, contrasted with that of stored plasma or serum, lies chiefly in its content of erythrocytes, and, secondly, that the real worth of these stored erythrocytes must lie in their ability to survive in the recipient's blood stream after transfusion. Nevertheless, most workers have accepted changes occurring in the erythrocytes *in vitro* as an indication of the value of a given method of preservation—in some cases, at least, assuming that such changes are correlated with *in vivo* survival. The changes most commonly measured are alterations in the osmotic fragility of the erythrocytes and the rate at which spontaneous haemolysis occurs during storage.

Criterion of Positive Value of Preservatives

The power to inhibit haemolysis during storage is certainly a desirable property in any preservative solution, since there are limits to the amount of haemolysed blood that may be safely injected into the blood stream. This, however, is a negative property, correlated with safety but not necessarily with value. The only procedure which seems to us to provide a criterion of the positive value of a given preservative solution is to follow the fate of the transfused erythrocytes in the recipient's blood stream. The *in vivo* survival may be measured by the differential agglutination method originally described by Ashby (1919). In brief, this consists in the transfusion of cells of Group O (IV) to a recipient of Group A (II). After transfusion the recipient's blood contains two types of cells, O and A. The A cells can be "removed" with anti-A serum and the free (O) cells counted. Actually a small fraction of the A cells are not agglutinated, and constitute a "blank" value to be deducted from the total of free cells. By counting the number of donor cells surviving at different intervals of

* Correcting the interpretation of an earlier observation (Lewis and Love, 1926).